Strong on results.

before Color-enhanced photo of *H. influenzae* seen through a scanning electron microscope.[5]

after *H. influenzae* culture after 24 hours' incubation with Bactrim (trimethoprim and sulfamethoxazole/Roche) at 5× MIC. Note long filaments and distorted shapes of bacteria.

ROCHE®

Simple to take.

In acute exacerbations of chronic bronchitis

- Clears susceptible pathogens from sputum[1-4]
- Reduces cough and sputum volume[1-4]
- Reduces evidence of inflammation[1]

Bactericidal *in vitro* against *H. influenzae* (nontypable strains)

Bactrim shows high activity *in vitro* against most strains of *H. influenzae*—even ampicillin-resistant strains. However, *in vitro* data do not necessarily correlate with clinical results.
In morphologic studies,[5] cultures of *H. influenzae* were exposed to Bactrim at 5× MIC. After just four hours, bacteria began to form filaments, indicating an alteration in the normal pattern of cell division. After 12 hours, virtually all bacteria had formed filaments. When these bacteria were removed and recultured in drug-free nutrient medium, almost all were unable to divide and form colonies—a result interpreted as demonstrating that, at the above concentration, the effect of Bactrim on the *H. influenzae* was bactericidal.

Also effective against susceptible strains of *S. pneumoniae in vitro*

In sputum cultures of *S. pneumoniae,* 91% of strains were susceptible to Bactrim.[6]
In acute exacerbations of chronic bronchitis involving *S. pneumoniae* or *H. influenzae,* sputum cultures taken seven days after a two-week course of therapy showed that Bactrim eradicated these bacteria in 91% (50 of 55) of the patients treated.[5]

Effective—and economical—antimicrobial therapy

In three double-blind studies, Bactrim DS *b.i.d.* was unsurpassed by ampicillin *q.i.d.*[1-3]
And in ten clinical comparisons with tetracycline involving nearly 700 patients, Bactrim proved comparable on major clinical parameters: change in sputum purulence, reduction in sputum volume and microbiological clearance of pathogens.[4]
And equally important: the convenient and economical *b.i.d.* dosage of Bactrim DS is designed to encourage patient compliance.

Bactrim™ DS

(trimethoprim and sulfamethoxazole/Roche)

Consistent success on a *b.i.d.* schedule

Please see references and summary of product information on following page.

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CORGARD®
(nadolol tablets)
ONCE A DAY FOR HYPERTENSION

CORGARD® TABLETS
Nadolol Tablets

DESCRIPTION: Corgard (nadolol) is a synthetic nonselective beta-adrenergic receptor blocking agent.

CONTRAINDICATIONS: Bronchial asthma, sinus bradycardia and greater than first degree conduction block, cardiogenic shock, and overt cardiac failure (see WARNINGS).

WARNINGS: Cardiac Failure — Sympathetic stimulation may be a vital component supporting circulatory function in congestive heart failure, and its inhibition by beta-blockade may precipitate more severe failure. Although beta-blockers should be avoided in overt congestive heart failure, if necessary, they can be used with caution in patients with a history of failure who are well-compensated, usually with digitalis and diuretics. Beta-adrenergic blocking agents do not abolish the inotropic action of digitalis on heart muscle. IN PATIENTS WITHOUT A HISTORY OF HEART FAILURE, continued use of beta-blockers can, in some cases, lead to cardiac failure; therefore, at first sign or symptom of heart failure, digitalize and/or give diuretics, and closely observe response, or discontinue nadolol (gradually if possible).

Exacerbation of Ischemic Heart Disease Following Abrupt Withdrawal — Hypersensitivity to catecholamines has been observed in patients withdrawn from beta-blocker therapy; exacerbation of angina and, in some cases, myocardial infarction have occurred after *abrupt* discontinuation of such therapy. When discontinuing chronic use of nadolol, particularly in patients with ischemic heart disease, gradually reduce dosage over a 1- to 2-week period and carefully monitor the patient. Reinstitute nadolol promptly (at least temporarily) and take other measures appropriate for management of unstable angina if angina markedly worsens or acute coronary insufficiency develops. Warn patients not to interrupt or discontinue therapy without physician's advice. Because coronary artery disease is common and may be unrecognized, it may be prudent not to discontinue nadolol therapy abruptly even in patients treated only for hypertension.

Nonallergic Bronchospasm (e.g., chronic bronchitis, emphysema) — PATIENTS WITH BRONCHOSPASTIC DISEASES SHOULD IN GENERAL NOT RECEIVE BETA-BLOCKERS. Administer nadolol with caution since it may block bronchodilation produced by endogenous or exogenous catecholamine stimulation of $beta_2$ receptors.

Major Surgery — Because beta blockade impairs the ability of the heart to respond to reflex stimuli and may increase risks of general anesthesia and surgical procedures, resulting in protracted hypotension or low cardiac output, it has generally been suggested that such therapy should be withdrawn several days prior to surgery. Recognition of the increased sensitivity to catecholamines of patients recently withdrawn from beta-blocker therapy, however, has made this recommendation controversial. If possible, withdraw beta-blockers well before surgery takes place. In emergency surgery, inform the anesthesiologist that the patient is on beta-blocker therapy. Use of beta-receptor agonists such as isoproterenol, dopamine, dobutamine, or levarterenol can reverse the effects of nadolol. Difficulty in restarting and maintaining the heart beat has also been reported with beta-adrenergic receptor blocking agents.

Diabetes and Hypoglycemia — Beta-adrenergic blockade may prevent the appearance of premonitory signs and symptoms (e.g., tachycardia and blood pressure changes) of acute hypoglycemia. This is especially important with labile diabetics. Beta-blockade also reduces release of insulin in response to hyperglycemia; therefore, it may be necessary to adjust dose of antidiabetic drugs.

Thyrotoxicosis — Beta-adrenergic blockade may mask certain clinical signs (e.g., tachycardia) of hyperthyroidism. To avoid abrupt withdrawal of beta-adrenergic blockade which might precipitate a thyroid storm, carefully manage patients suspected of developing thyrotoxicosis.

PRECAUTIONS: Impaired Hepatic or Renal Function — Use nadolol with caution in presence of either of these conditions (see DOSAGE AND ADMINISTRATION section of package insert).

Information for Patients — Warn patients, especially those with evidence of coronary artery insufficiency, against interruption or discontinuation of nadolol without physician's advice. Although cardiac failure rarely occurs in properly selected patients, advise patients being treated with beta-adrenergic blocking agents to consult physician at first sign or symptom of impending failure.

Drug Interactions — Catecholamine-depleting drugs (e.g., reserpine) may have an additive effect when given with beta-blocking agents. When treating patients with nadolol plus a catecholamine-depleting agent, carefully observe for evidence of hypotension and/or excessive bradycardia which may produce vertigo, syncope, or postural hypotension.

Carcinogenesis, Mutagenesis, Impairment of Fertility — In 1 to 2 years' oral toxicologic studies in mice, rats, and dogs, nadolol did not produce significant toxic effects. In 2-year oral carcinogenic studies in rats and mice, nadolol did not produce neoplastic, preneoplastic, or nonneoplastic pathologic lesions.

Pregnancy — In animal reproduction studies with nadolol, evidence of embryo- and fetotoxicity was found in rabbits (but not in rats or hamsters) at doses 5 to 10 times greater (on a mg/kg basis) than maximum indicated human dose; no teratogenic potential was seen in any of these species. There are no well-controlled studies in pregnant women; therefore, use nadolol in pregnant women only if potential benefit justifies potential risk to the fetus.

Nursing Mothers — It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, exercise caution when nadolol is administered to a nursing woman. Animal studies showed that nadolol is found in the milk of lactating rats.

Pediatric Use — Safety and effectiveness in children have not been established.

ADVERSE REACTIONS: Most adverse effects have been mild and transient and have rarely required nadolol withdrawal.

Cardiovascular — Bradycardia with heart rates of less than 60 beats per minute occurs commonly, and heart rates below 40 beats per minute and/or symptomatic bradycardia were seen in about 2 of 100 patients. Symptoms of peripheral vascular insufficiency, usually of the Raynaud type, have occurred in approximately 2 of 100 patients. Cardiac failure, hypotension, and rhythm/conduction disturbances have each occurred in about 1 of 100 patients. Single instances of first degree and third degree heart block have been reported; intensification of AV block is a known effect of beta-blockers (see also CONTRAINDICATIONS, WARNINGS, and PRECAUTIONS). **Central Nervous System —** Dizziness or fatigue reported in approximately 2 of 100 patients; paresthesias, sedation, and change in behavior reported in approximately 6 of 1000 patients. **Respiratory —** Bronchospasm reported in approximately 1 of 1000 patients (see CONTRAINDICATIONS and WARNINGS). **Gastrointestinal —** Nausea, diarrhea, abdominal discomfort, constipation, vomiting, indigestion, anorexia, bloating, and flatulence each reported in 1 to 5 of 1000 patients. **Miscellaneous —** Each of the following reported in 1 to 5 of 1000 patients: rash; pruritus; headache; dry mouth, eyes, or skin; impotence or decreased libido; facial swelling; weight gain; slurred speech; cough; nasal stuffiness; sweating; tinnitus; blurred vision. Although relationship to drug usage is not clear, sleep disturbances have been reported. The oculomucocutaneous syndrome associated with practolol has not been reported with nadolol.

Potential Adverse Effects: Although other adverse effects reported with other beta-adrenergic blocking agents have not been reported with nadolol, they should be considered potential adverse effects of nadolol. **Central Nervous System —** reversible mental depression progressing to catatonia; visual disturbances; hallucinations; an acute reversible syndrome characterized by disorientation for time and place; short-term memory loss, emotional lability with slightly clouded sensorium; decreased performance on neuropsychometrics. **Gastrointestinal —** mesenteric arterial thrombosis; ischemic colitis. **Hematologic —** agranulocytosis; thrombocytopenic or nonthrombocytopenic purpura. **Allergic —** fever combined with aching and sore throat; laryngospasm; respiratory distress. **Miscellaneous —** reversible alopecia; Peyronie's disease; erythematous rash.

OVERDOSAGE: Nadolol can be removed from the general circulation by hemodialysis. In addition to gastric lavage, employ the following measures as appropriate. In determining duration of corrective therapy, take note of long duration of effect of nadolol.

Excessive Bradycardia — Administer atropine (0.25 to 1.0 mg). If there is no response to vagal blockade, administer isoproterenol cautiously.

Cardiac Failure — Administer a digitalis glycoside and diuretic. It has been reported that glucagon may also be useful in this situation.

Hypotension — Administer vasopressors, e.g., epinephrine or levarterenol. (There is evidence that epinephrine may be the drug of choice.)

Bronchospasm — Administer a $beta_2$-stimulating agent and/or a theophylline derivative.

DOSAGE: For all patients, DOSAGE MUST BE INDIVIDUALIZED.

For **angina pectoris,** usual initial dose is 40 mg q.d.; gradually increase in 40 to 80 mg increments at 3 to 7 day intervals until optimum clinical response or pronounced slowing of the heart rate; usual maintenance dose is 80 to 240 mg q.d. (most patients respond to 160 mg or less daily). If treatment is to be discontinued, reduce dosage gradually over a period of 1 to 2 weeks (see WARNINGS).

For **hypertension,** usual initial dose is 40 mg q.d.; gradually increase in 40 to 80 mg increments until optimum blood pressure reduction is achieved; usual maintenance dose is 80 to 320 mg q.d. (rarely, doses up to 640 mg may be needed).

Patients with renal failure require adjustment in dosing interval; see package insert for dosage in these patients.

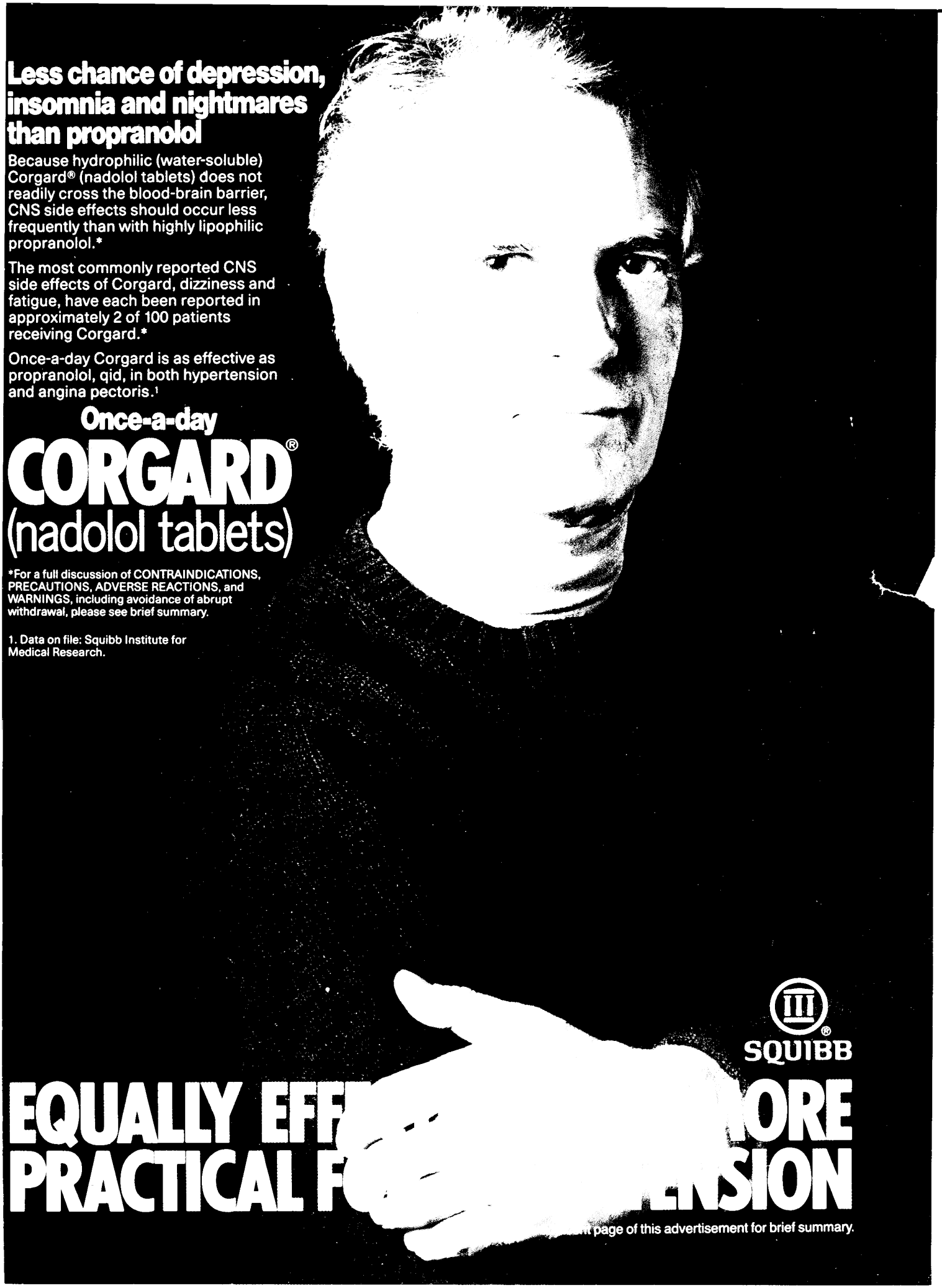
For full prescribing information, consult package insert.

HOW SUPPLIED: In scored tablets containing 40, 80, 120, or 160 mg nadolol per tablet in bottles of 100 and 1000 tablets and in Unimatic® unit-dose packs of 100 tablets. The 40 mg and 80 mg tablets are also available in convenience packages containing 4 blister cards of 7 tablets each.

SQUIBB

513-513

Issued: July 1983


Less chance of depression, insomnia and nightmares than propranolol
Because hydrophilic (water-soluble) Corgard® (nadolol tablets) does not readily cross the blood-brain barrier, CNS side effects should occur less frequently than with highly lipophilic propranolol.*
The most commonly reported CNS side effects of Corgard, dizziness and fatigue, have each been reported in approximately 2 of 100 patients receiving Corgard.*
Once-a-day Corgard is as effective as propranolol, qid, in both hypertension and angina pectoris.1
Once-a-day
CORGARD®
(nadolol tablets)
*For a full discussion of CONTRAINDICATIONS, PRECAUTIONS, ADVERSE REACTIONS, and WARNINGS, including avoidance of abrupt withdrawal, please see brief summary.
1. Data on file: Squibb Institute for Medical Research.
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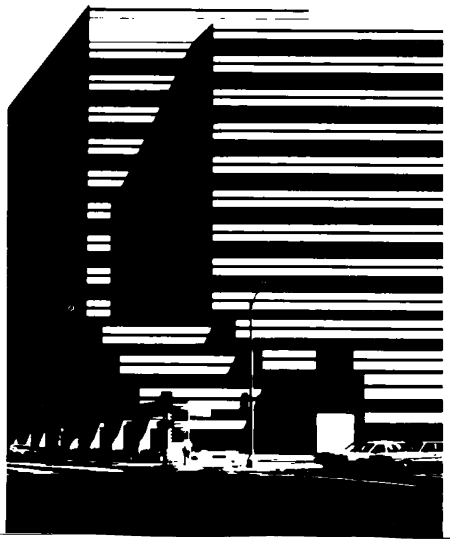

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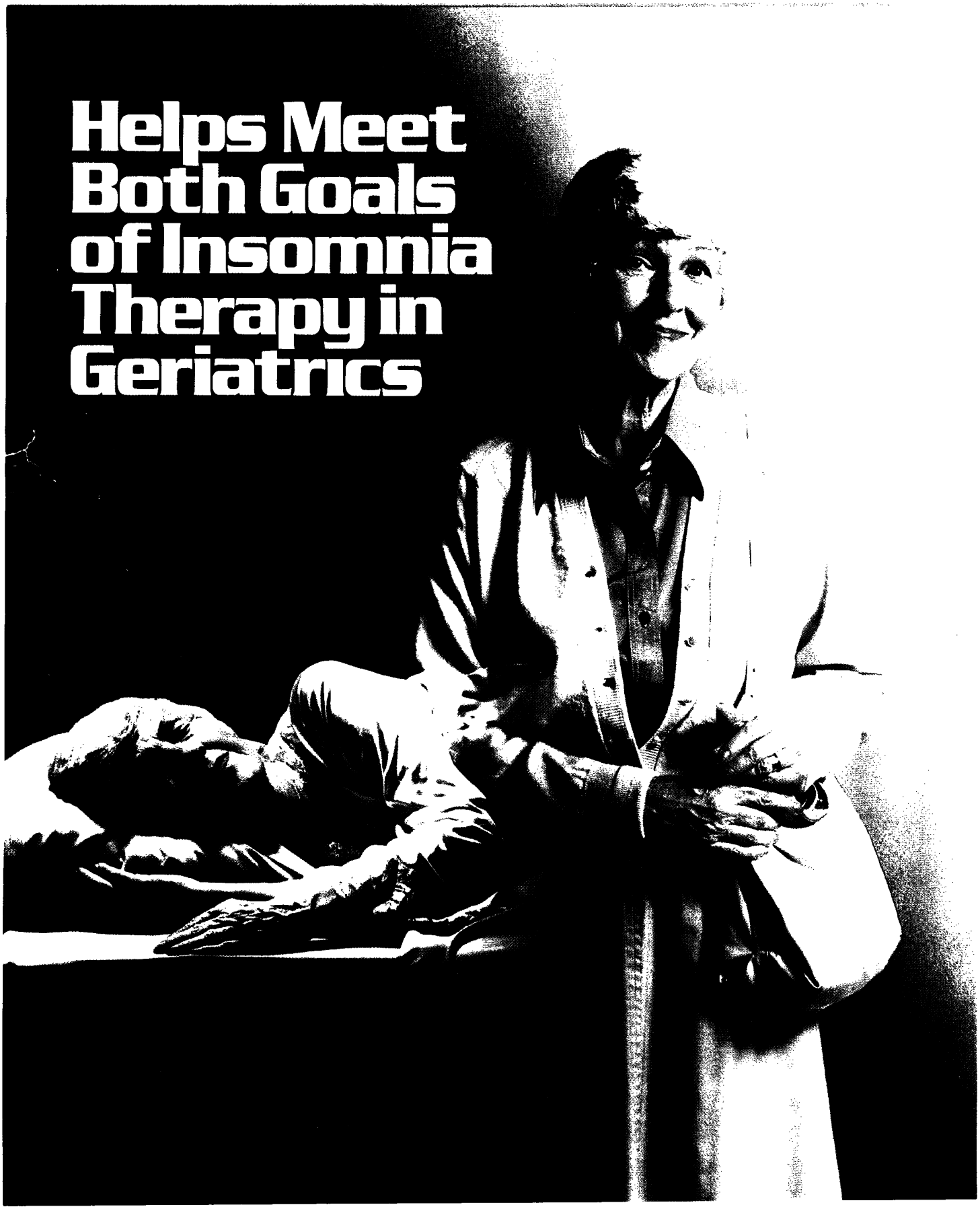
Halcion® 0.25 mg Tablets
triazolam Ⓒ IV

Helps Meet Both Goals of Insomnia Therapy in Geriatrics



Upjohn Please see next page for brief summary of prescribing information.

Goal 1: Improved Sleep
Better Initiation and Maintenance of Sleep

- *Halcion* was found to initiate sleep in insomniac patients *within 17.4 minutes* after ingestion.
- Peak serum concentration occurs at 1.3 hours.
- Patients receiving *Halcion* were found to have 56.9% *fewer nighttime awakenings* (compared with baseline).
- Patients receiving *Halcion slept longer* each night of therapy (an average of 36 minutes longer) in comparison with baseline.

Goal 2: Daytime Alertness
Better Morning and Daytime Alertness

- *Halcion* has the shortest half-life of any benzodiazepine-derived sleep medication.
- In controlled studies, *Halcion* treated patients demonstrated *significantly better* morning and daytime alertness than flurazepam-treated patients.[1]
- Within 24 hours following a single oral dose, *Halcion* was *no longer detectable* in the plasma.
- Patients receiving *Halcion* should be cautioned about the possible combined effects with alcohol and other CNS depressants.

RAPIDLY ABSORBED FOR IMPROVED SLEEP

PROMPTLY EXCRETED FOR DAYTIME ALERTNESS

Halcion
triazolam (IV)

0.25 mg tablets
Initiate at 0.125 mg

Halcion Tablets
triazolam C-IV

Special Dosage Guidelines for Geriatric Patients

0.125 MG TO 0.25 MG
Initiate at 0.125 mg (half of a 0.25 mg scored tablet) until individual response is determined.

Because geriatric and/or debilitated patients respond favorably to lower doses of *Halcion*, initiation at the above dosage is recommended.

DOSAGE FOR NON-GERIATRIC PATIENTS: 0.25 MG TO 0.5 MG

Patients should be advised against engaging in hazardous tasks that require mental alertness (operating machinery or driving a motor vehicle).

Reference: 1. Ogura C, et al: Residual effects of hypnotics: Triazolam, flurazepam, and nitrazepam. *Psychopharmacol* 1980; 68:61-65.

Halcion Tablets
triazolam C-IV

INDICATIONS AND USAGE
HALCION Tablets are indicated in the short-term management of insomnia characterized by difficulty in falling asleep, frequent nocturnal awakenings, and/or early morning awakenings.

It is recommended that HALCION not be prescribed in quantities exceeding a one-month supply.

CONTRAINDICATIONS
Patients with known hypersensitivity to this drug or other benzodiazepines.

HALCION is contraindicated in pregnant women due to potential fetal damage. Patients likely to become pregnant while receiving HALCION should be warned of the potential risk to the fetus.

WARNINGS
Overdosage may occur at 2 mg, four times the maximum recommended therapeutic dose (0.5 mg). Patients should be cautioned not to exceed prescribed dosage.

Because of its depressant CNS effects, patients should be cautioned against engaging in hazardous occupations requiring complete mental alertness and also about the simultaneous ingestion of alcohol and other CNS depressant drugs.

Anterograde amnesia and paradoxical reactions have been reported with HALCION and some other benzodiazepines.

PRECAUTIONS
General: In elderly and/or debilitated patients, treatment should be initiated at 0.125 mg to decrease the possibility of development of oversedation, dizziness, or impaired coordination. Caution should be exercised in patients with signs or symptoms of depression which could be intensified by hypnotic drugs. Suicidal tendencies and intentional overdosage is more common in these patients. The usual precautions should be observed in patients with impaired renal or hepatic function and chronic pulmonary insufficiency. Information for Patients: Alert patients about: (a) consumption of alcohol and drugs, (b) possible fetal abnormalities, (c) operating machinery or driving, (d) not increasing dose of the drug due to risk of dependence, (e) possible worsening of sleep after discontinuing HALCION. Laboratory Tests: Not ordinarily required in otherwise healthy patients. Drug Interactions: Additive CNS depressant effects with other psychotropics, anticonvulsants, antihistaminics, ethanol, and other CNS depressants. Pharmacokinetic interactions of benzodiazepines with other drugs have been reported. Carcinogenesis, Mutagenesis, Impairment of Fertility: No evidence of carcinogenic potential was observed in mice during a 24-month study with HALCION in doses up to 4000 times the human dose. Pregnancy: Benzodiazepines may cause fetal damage if administered during pregnancy. The child born of a mother who is on benzodiazepines may be at some risk for withdrawal symptoms and neonatal flaccidity during the postnatal period. Nursing Mothers: Administration to nursing mothers is not recommended. Pediatric Use: Safety and efficacy in children below the age of 18 have not been established.

ADVERSE REACTIONS
During placebo-controlled clinical studies in which 1003 patients received HALCION Tablets, the most troublesome side effects were extensions of the pharmacologic activity of HALCION, e.g. drowsiness, dizziness, or lightheadedness.

	HALCION	Placebo
Number of Patients	1003	997
% of Patients Reporting:		
Central Nervous System		
Drowsiness	14.0	6.4
Headache	9.7	8.4
Dizziness	7.8	3.1
Nervousness	5.2	4.5
Lightheadedness	4.9	0.9
Coordination Disorder/Ataxia	4.6	0.8
Gastrointestinal		
Nausea/Vomiting	4.6	3.7

In addition, the following adverse events have been reported less frequently (i.e., 0.9-0.5%): euphoria, tachycardia, tiredness, confusional states/memory impairment, cramps/pain, depression, visual disturbances.

Rare (i.e., less than 0.5%) adverse reactions included constipation, taste alterations, diarrhea, dry mouth, dermatitis/allergy, dreaming/nightmares, insomnia, paresthesia, tinnitus, dysesthesia, weakness, congestion, death from hepatic failure in a patient also receiving diuretic drugs.

The following adverse events have been reported in association with the use of benzodiazepines: dystonia, irritability, anorexia, fatigue, sedation, slurred speech, jaundice, pruritus, dysarthria, changes in libido, menstrual irregularities, incontinence and urinary retention.

As with all benzodiazepines, paradoxical reactions such as stimulation, agitation, increased muscle spasticity, sleep disturbances, hallucinations and other adverse behavioral effects may occur rarely and in a random fashion. Should these occur, use of the drug should be discontinued.

No laboratory changes were considered to be of physiological significance.

When treatment is protracted, periodic blood counts, urinalysis and blood chemistry analyses are advisable.

Minor changes in EEG patterns, usually low-voltage fast activity have been observed in patients during HALCION therapy and are of no known significance.

DRUG ABUSE AND DEPENDENCE
Controlled Substance: HALCION Tablets are a Controlled Substance in Schedule IV. Abuse and Dependence: Withdrawal symptoms have occurred following abrupt discontinuance of benzodiazepines. Patients with a history of seizures are at particular risk. Addiction-prone patients should be closely monitored. Repeat prescriptions should be limited to those under medical supervision.

OVERDOSAGE
Because of the potency of triazolam, overdosage may occur at 2 mg, four times the maximum recommended therapeutic dose (0.5 mg). Manifestations of overdosage include somnolence, confusion, impaired coordination, slurred speech, and ultimately, coma. Respiration, pulse, and blood pressure should be monitored and supported by general measures when necessary. Immediate gastric lavage should be performed. Multiple agents may have been ingested.

Store at controlled room temperature 15°-30°C (59°-86°F).

Caution: Federal law prohibits dispensing without prescription.

J-3671R October 1983

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Kalamazoo, Michigan 49001 USA


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Pfizer

Navane®
(thiothixene) (thiothixene HCl)

References: 1. Util TM, Unverdi C. Wohlrade J, et al: Drug therapy of psychosis associated with organic brain syndrome. Presented as a Scientific Exhibit at the American Public Health Association Centennial, Atlantic City, New Jersey, November 12-16, 1972. 2. Katz MM, Util TM: Video methodology for research in psychopathology and psychopharmacology. *Arch Gen Psychiatry* 31:204-210, 1974. 3. Ketai R: Psychotropic drugs in the management of psychiatric emergencies. *Postgraduate Medicine* 58:87-93, 1975. 4. Birkett DP, Hirschfield W, Simpson GM: Thiothixene in the treatment of diseases of the senium. *Curr Ther Res* 14:775-779, 1972. 5. Data on file at Roerig.

BRIEF SUMMARY OF PRESCRIBING INFORMATION
Navane® (thiothixene) Capsules: 1 mg, 2 mg, 5 mg, 10 mg, 20 mg
(thiothixene hydrochloride) Concentrate: 5 mg/ml, Intramuscular: 2 mg/ml, 5 mg/ml

Contraindications: Navane (thiothixene) is contraindicated in patients with circulatory collapse, comatose states, central nervous system depression due to any cause, and blood dyscrasias. Navane is contraindicated in individuals who have shown hypersensitivity to the drug. It is not known whether there is a cross-sensitivity between the thioxanthenes and the phenothiazine derivatives, but the possibility should be considered.

Warnings: *Usage in Pregnancy* – Safe use of Navane during pregnancy has not been established. Therefore, this drug should be given to pregnant patients only when, in the judgment of the physician, the expected benefits from the treatment exceed the possible risks to mother and fetus. Animal reproduction studies and clinical experience to date have not demonstrated any teratogenic effects.

In the animal reproduction studies with Navane, there was some decrease in conception rate and litter size, and an increase in resorption rate in rats and rabbits, changes which have been similarly reported with other psychotropic agents. After repeated oral administration of Navane to rats (5 to 15 mg/kg/day), rabbits (3 to 50 mg/kg/day), and monkeys (1 to 3 mg/kg/day) before and during gestation, no teratogenic effects were seen. (See Precautions.)

Usage in Children – The use of Navane in children under 12 years of age is not recommended because safety and efficacy in the pediatric age group have not been established.

As is true with many CNS drugs, Navane may impair the mental and/or physical abilities required for the performance of potentially hazardous tasks such as driving a car or operating machinery, especially during the first few days of therapy. Therefore, the patient should be cautioned accordingly.

As in the case of other CNS-acting drugs, patients receiving Navane should be cautioned about the possible additive effects (which may include hypotension) with CNS depressants and with alcohol.

Precautions: An antiemetic effect was observed in animal studies with Navane, since this effect may also occur in man, it is possible that Navane may mask signs of overdosage of toxic drugs and may obscure conditions such as intestinal obstruction and brain tumor.

In consideration of the known capability of Navane and certain other psychotropic drugs to precipitate convulsions, extreme caution should be used in patients with a history of convulsive disorders or those in a state of alcohol withdrawal since it may lower the convulsive threshold. Although Navane potentiates the actions of the barbiturates, the dosage of the anticonvulsant therapy should not be reduced when Navane is administered concurrently.

Caution as well as careful adjustment of the dosage is indicated when Navane is used in conjunction with other CNS depressants other than anticonvulsant drugs.

Though exhibiting rather weak anticholinergic properties, Navane should be used with caution in patients who are known or suspected to have glaucoma, or who might be exposed to extreme heat, or who are receiving atropine or related drugs.

Use with caution in patients with cardiovascular disease.

Also, careful observation should be made for pigmentary retinopathy, and lenticular pigmentation (fine lenticular pigmentation has been noted in a small number of patients treated with Navane for prolonged periods). Blood dyscrasias (agranulocytosis, pancytopenia, thrombocytopenic purpura), and liver damage (jaundice, biliary stasis) have been reported with related drugs.

Undue exposure to sunlight should be avoided. Photosensitive reactions have been reported in patients on Navane.

Neuroleptic drugs elevate prolactin levels; the elevation persists during chronic administration. Tissue culture experiments indicate that approximately one-third of human breast cancers are prolactin dependent *in vitro*, a factor of potential importance if the prescription of these drugs is contemplated in a patient with a previously detected breast cancer. Although disturbances such as galactorrhea, amenorrhea, gynecomastia, and impotence have been reported, the clinical significance of elevated serum prolactin levels is unknown for most patients. An increase in mammary neoplasms has been found in rodents after chronic administration of neuroleptic drugs. Neither clinical studies nor epidemiologic studies conducted to date, however, have shown an association between chronic administration of these drugs and mammary tumorigenesis; the available evidence is considered too limited to be conclusive at this time.

Intramuscular Administration – As with all intramuscular preparations, Navane Intramuscular should be injected well within the body of a relatively large muscle. The preferred sites are the upper outer quadrant of the buttock (i.e. gluteus maximus) and the mid-lateral thigh.

The deltoid area should be used only if well developed, such as in certain adults and older children, and then only with caution to avoid radial nerve injury. Intramuscular injections should not be made into the lower and mid-thirds of the upper arm. As with all intramuscular injections, aspiration is necessary to help avoid inadvertent injection into a blood vessel.

Adverse Reactions: *Note:* Not all of the following adverse reactions have been reported with Navane (thiothixene). However, since Navane has certain chemical and pharmacologic similarities to the phenothiazines, all of the known side effects and toxicity associated with phenothiazine therapy should be borne in mind when Navane is used.

Cardiovascular effects: Tachycardia, hypotension, lightheadedness, and syncope. In the event hypotension occurs, epinephrine should not be used as a pressor agent since a paradoxical further lowering of blood pressure may result. Nonspecific EKG changes have been observed in some patients receiving Navane. These changes are usually reversible and frequently disappear on continued Navane therapy. The incidence of these changes is lower than that observed with some phenothiazines. The clinical significance of these changes is not known.

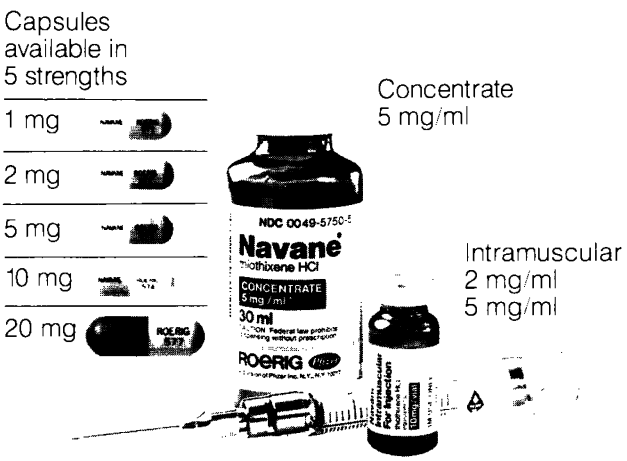
CNS effects: Drowsiness, usually mild, may occur although it usually subsides with continuation of Navane therapy. The incidence of sedation appears similar to that of the piperazine group of phenothiazines, but less than that of certain aliphatic phenothiazines. Restlessness, agitation and insomnia have been noted with Navane (thiothixene). Seizures and paradoxical exacerbation of psychotic symptoms have occurred with Navane infrequently.

Hyperreflexia has been reported in infants delivered from mothers having received structurally related drugs.

In addition, phenothiazine derivatives have been associated with cerebral edema and cerebrospinal fluid abnormalities.

Extrapyramidal symptoms, such as pseudo-parkinsonism, akathisia, and dystonia have been reported. Management of these extrapyramidal symptoms depends upon the type and severity. Rapid relief of acute symptoms may require the use of an injectable antiparkinson agent. More slowly emerging symptoms may be managed by reducing the dosage of Navane and/or administering an oral antiparkinson agent.

Persistent Tardive Dyskinesia: As with all antipsychotic agents tardive dyskinesia may appear in some patients on long term therapy or may occur after drug therapy has been discontinued. The risk seems to be greater in elderly patients on high-dose therapy, especially females. The symptoms are persistent and in some patients appear to be irreversible. The syndrome is characterized by rhythmical involuntary movements of the tongue, face, mouth or jaw (e.g., protrusion of tongue, puffing of cheeks, puckering of mouth, chewing movements). Sometimes these may be accompanied by involuntary movements of extremities.



There is no known effective treatment for tardive dyskinesia; antiparkinsonism agents usually do not alleviate the symptoms of this syndrome. It is suggested that all antipsychotic agents be discontinued if these symptoms appear.

Should it be necessary to reinstitute treatment, or increase the dosage of the agent, or switch to a different antipsychotic agent, the syndrome may be masked.

It has been reported that fine vermicular movements of the tongue may be an early sign of the syndrome and if the medication is stopped at that time, the syndrome may not develop.

Hepatic effects: Elevations of serum transaminase and alkaline phosphatase, usually transient, have been infrequently observed in some patients. No clinically confirmed cases of jaundice attributable to Navane (thiothixene) have been reported.

Hematologic effects: As is true with certain other psychotropic drugs, leukopenia and leukocytosis, which are usually transient, can occur occasionally with Navane. Other antipsychotic drugs have been associated with agranulocytosis, eosinophilia, hemolytic anemia, thrombocytopenia and pancytopenia.

Allergic reactions: Rash, pruritus, urticaria, photosensitivity and rare cases of anaphylaxis have been reported with Navane. Undue exposure to sunlight should be avoided. Although not experienced with Navane, exfoliative dermatitis and contact dermatitis (in nursing personnel) have been reported with certain phenothiazines.

Endocrine disorders: Lactation, moderate breast enlargement and amenorrhea have occurred in a small percentage of females receiving Navane. If persistent, this may necessitate a reduction in dosage or the discontinuation of therapy. Phenothiazines have been associated with false positive pregnancy tests, gynecomastia, hypoglycemia, hyperglycemia, and glycosuria.

Autonomic effects: Dry mouth, blurred vision, nasal congestion, constipation, increased sweating, increased salivation, and impotence have occurred infrequently with Navane therapy. Phenothiazines have been associated with miosis, mydriasis, and adynamic ileus.

Other adverse reactions: Hyperpyrexia, anorexia, nausea, vomiting, diarrhea, increase in appetite and weight, weakness or fatigue, polydipsia and peripheral edema.

Although not reported with Navane, evidence indicates there is a relationship between phenothiazine therapy and the occurrence of a systemic lupus erythematosus-like syndrome.

NOTE: Sudden deaths have occasionally been reported in patients who have received certain phenothiazine derivatives. In some cases the cause of death was apparently cardiac arrest or asphyxia due to failure of the cough reflex. In others, the cause could not be determined nor could it be established that death was due to phenothiazine administration.

Dosage and Administration: Dosage of Navane should be individually adjusted depending on the chronicity and severity of the condition. In general, small doses should be used initially and gradually increased to the optimal effective level, based on patient response.

Some patients have been successfully maintained on once-a-day Navane therapy.

Usage in children under 12 years of age is not recommended because safe conditions for its use have not been established.

Navane Intramuscular Solution: Navane For Injection – Where more rapid control and treatment of acute behavior is desirable, the intramuscular form of Navane may be indicated. It is also of benefit where the very nature of the patient's symptomatology, whether acute or chronic, renders oral administration impractical or even impossible.

For treatment of acute symptomatology or in patients unable or unwilling to take oral medication, the usual dose is 4 mg of Navane Intramuscular administered 2 to 4 times daily. Dosage may be increased or decreased depending on response. Most patients are controlled on a total daily dosage of 16 to 20 mg. The maximum recommended dosage is 30 mg/day. An oral form should supplant the injectable form as soon as possible. It may be necessary to adjust the dosage when changing from the intramuscular to oral dosage forms. Dosage recommendations for Navane (thiothixene) Capsules and Concentrate appear in the following paragraphs.

Navane Capsules: Navane Concentrate – In milder conditions, an initial dose of 2 mg three times daily. If indicated, a subsequent increase to 15 mg/day total daily dose is often effective.

In more severe conditions, an initial dose of 5 mg twice daily.

The usual optimal dose is 20 to 30 mg daily. If indicated, an increase to 60 mg/day total daily dose is often effective. Exceeding a total daily dose of 60 mg rarely increases the beneficial response.

Overdosage: Manifestations include muscular twitching, drowsiness, and dizziness. Symptoms of gross overdosage may include CNS depression, rigidity, weakness, torticollis, tremor, salivation, dysphagia, hypotension, disturbances of gait, or coma.

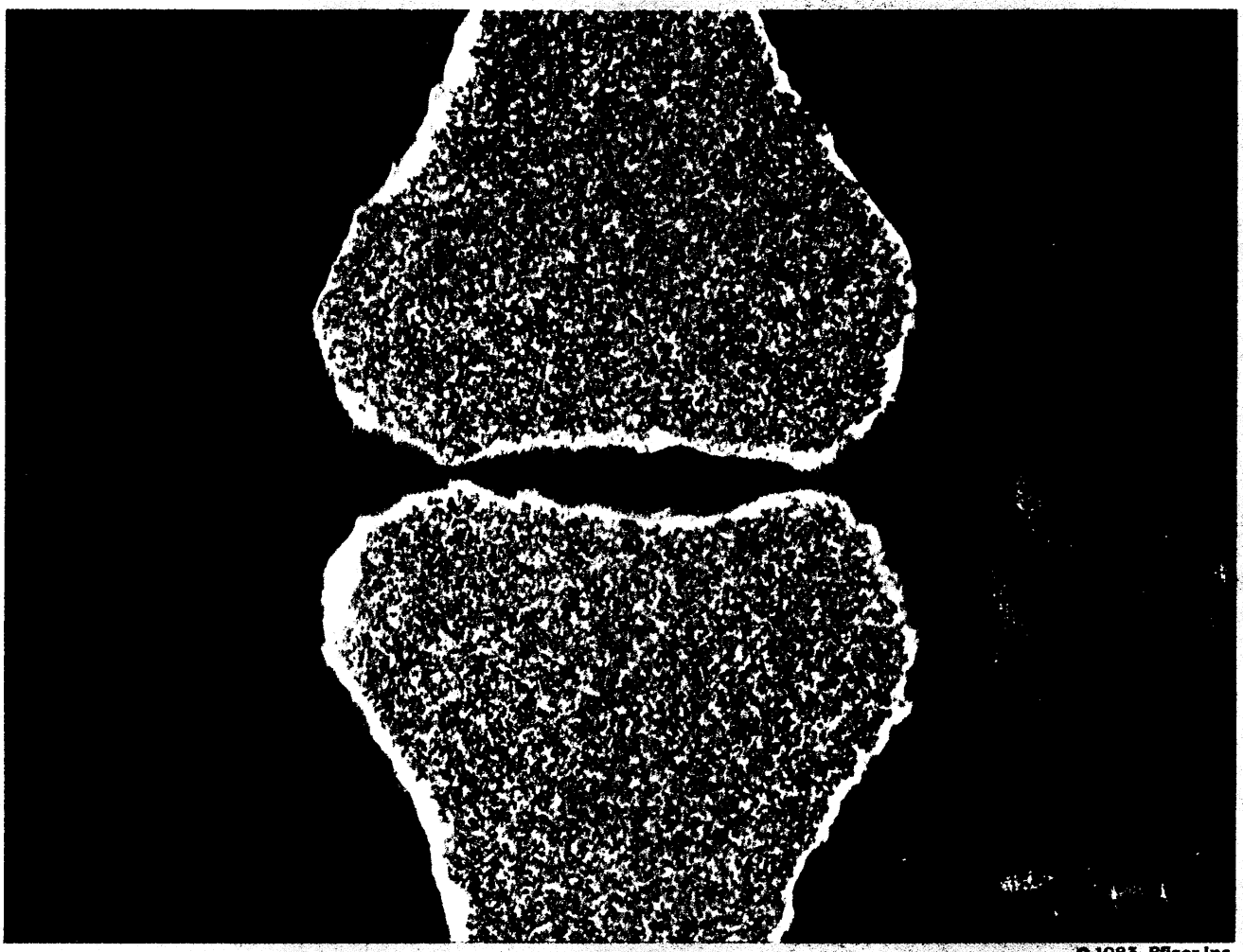
Treatment: Essentially is symptomatic and supportive. For Navane oral, early gastric lavage is helpful. For Navane oral and Intramuscular, keep patient under careful observation and maintain an open airway, since involvement of the extrapyramidal system may produce dysphagia and respiratory difficulty in severe overdosage. If hypotension occurs, the standard measures for managing circulatory shock should be used (I.V. fluids and/or vasoconstrictors.)

If a vasoconstrictor is needed, levarterenol and phenylephrine are the most suitable drugs. Other pressor agents, including epinephrine, are not recommended, since phenothiazine derivatives may reverse the usual pressor action of these agents and cause further lowering of the blood pressure.

If CNS depression is present and specific therapy is indicated, recommended stimulants include amphetamine, dextroamphetamine, or caffeine and sodium benzoate. Stimulants that may cause convulsions (e.g. picrotoxin or pentylenetetrazol) should be avoided. Extrapyramidal symptoms may be treated with antiparkinson drugs.

There are no data on the use of peritoneal or hemodialysis, but they are known to be of little value in phenothiazine intoxication.

ROERIG Pfizer
A division of Pfizer Pharmaceuticals



This is how an arthritis patient's joints often feel.

You can help these patients feel better with one-a-day FELDENE (piroxicam).
For good reasons:

- it's effective—proven relief of the pain and inflammation of rheumatoid arthritis and osteoarthritis in millions of patients, in 80 countries all around the world.
- it's efficient—once daily, 20-mg dose provides round-the-clock relief, improves compliance and remains effective during long-term therapy, maintaining 24-hour therapeutic blood levels once steady state is reached in 7 to 12 days.
- it's preferred—in an open multi-center study, the antiarthritic preferred by physicians for their patients was FELDENE.[1]

Feldene® *ONE-A-DAY*

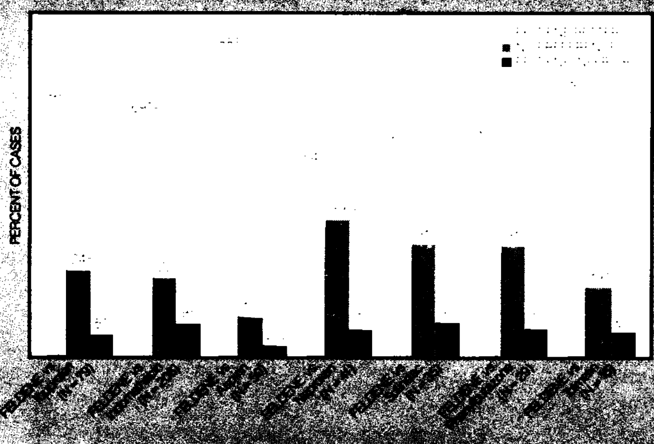
(PIROXICAM) 20 mg capsules

Please see a brief summary of FELDENE (piroxicam) prescribing information on the following page.

Feldene®
(PIROXICAM) 20 mg capsules

Rated better by physicians in an open multicenter trial

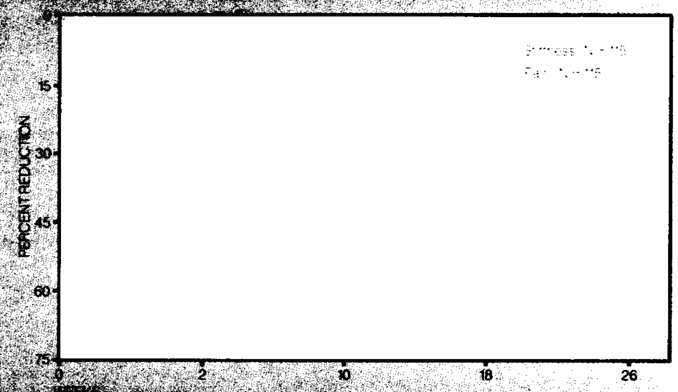
INVESTIGATORS' COMPARATIVE GLOBAL EVALUATIONS
(Physicians rated Feldene therapy as "better than," "equal to," or "inferior to" previous therapy based on global evaluations of patients' overall response.)



(Adapted from Dessain P, in Postgrad Med, April 1982[1])

Investigators' global comparisons of Feldene and previous medications in multicenter open trials by 158 physicians in 748 osteoarthritis patients who had been on previous drug therapy. The above chart includes only those drugs available in the U.S. Average FELDENE dose was 20 mg/day.

REDUCTION IN PAIN AND STIFFNESS
Patients with osteoarthritis evaluated over 6 months on Feldene (mean dose of 20 mg/day) therapy showed dramatic reduction in pain and stiffness.



(Adapted from Dessain P, in Postgrad Med, April 1982[1])

Multicenter long-term follow-up of 154 patients who had shown adequate response to piroxicam in short-term trials. 115 patients for whom complete data were available at every assessment visit through 26 weeks.

Reference:
1. Dessain P: Efficacy and tolerance of piroxicam in general practice: A multicenter study of osteoarthritis. Postgrad Med (special report), 78–81, April, 1982.

Brief Summary
FELDENE® (piroxicam) Capsules

[illegible]

...in pregnant women because of the [illegible] in humans.

[illegible] in children have not been established.

ADVERSE REACTIONS: [illegible] piroxicam is based on clinical trials involv- [illegible] for more than one year and 170 for more [illegible] 20 mg of FELDENE experienced side effects. [illegible] occurring in approximately 20% of the pa- [illegible] with an overall incidence of peptic ulceration [illegible]

[illegible] frequently than 1 in 100.

[illegible] constipation, abdominal discomfort, [illegible] (see PRECAUTIONS), leucopenia, eosinophilia [illegible]

[illegible] vomiting, hematemesis, melena, gas- [illegible] erythema multiforme, toxic epidermal necro- [illegible]

[illegible] of less than 1 in 100, but a causal relationship between [illegible]

OVERDOSAGE: [illegible] the long plasma half-life of piroxicam should [illegible] characterization of sequelae and re- [illegible] It is reasonable to assume that the standard measures [illegible]

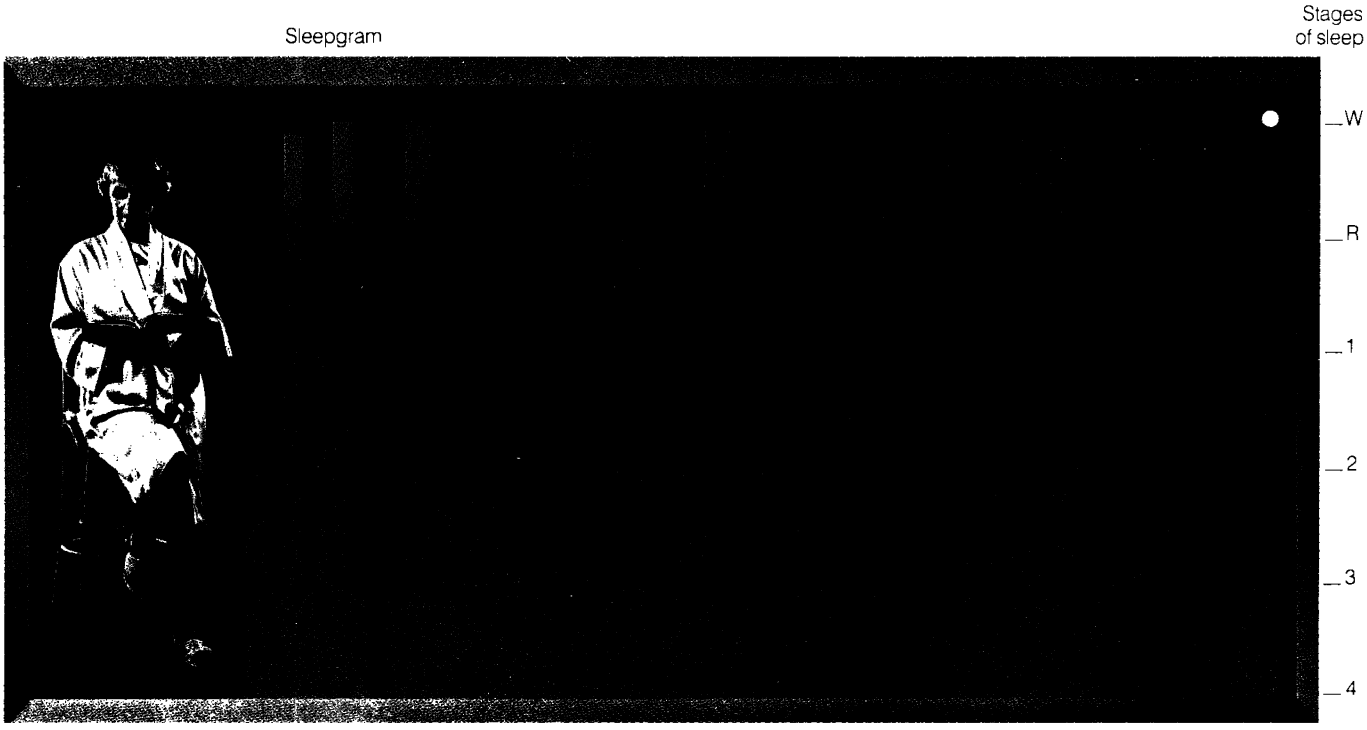
DOSAGE AND ADMINISTRATION: [illegible] It is recommended that FELDENE [illegible] 20 mg. If desired, the daily dose may be divided. [illegible] are not reached for 7-12 days. Therefore, [illegible] there is a progressive increase in [illegible] should not be assessed for two weeks. [illegible] in children have not been established.

More detailed professional information available on request.

Pfizer LABORATORIES DIVISION
Pfizer Inc.

ISRUPTIVE
ISTRESSING
ISABLING

THE DISRUPTIVE PATTERN OF VASOMOTOR SYMPTOMS



The sleepgram demonstrates the correlation between hot flushes and waking episodes that can disrupt the menopausal woman's sleep night after night. —adapted from Erlik et al, p 1742.[1]

■ = objectively measured hot flush
o = arousal of patient by investigator at end of the study
W = Waking
R = Rapid Eye Movement (REM)

EFFECTIVE TREATMENT

Hot flushes, with associated immediate-waking episodes, can occur several times a night—severely disrupting the menopausal patient's sleep.[2] The symptoms may also appear during the day and seriously disrupt the patient's life.

Scientific evidence has shown that the symptoms are not purely subjective.[2] In one study, nearly all objectively recorded hot flushes during sleep were associated with immediate waking episodes.[1] They're the most common cause for which menopausal patients seek medical attention.[2] At least 75% of menopausal women experience the symptoms, which persist for over one year in 80% of those afflicted. But 25% to 50% of the women suffer longer than five years.[3]

PREMARIN® (Conjugated Estrogens Tablets, U.S.P.) therapy is effective in reducing the severity and frequency of symptomatic attacks and eliminating them altogether. When moderate to severe vasomotor symptoms are chronically disruptive, provide relief with PREMARIN.

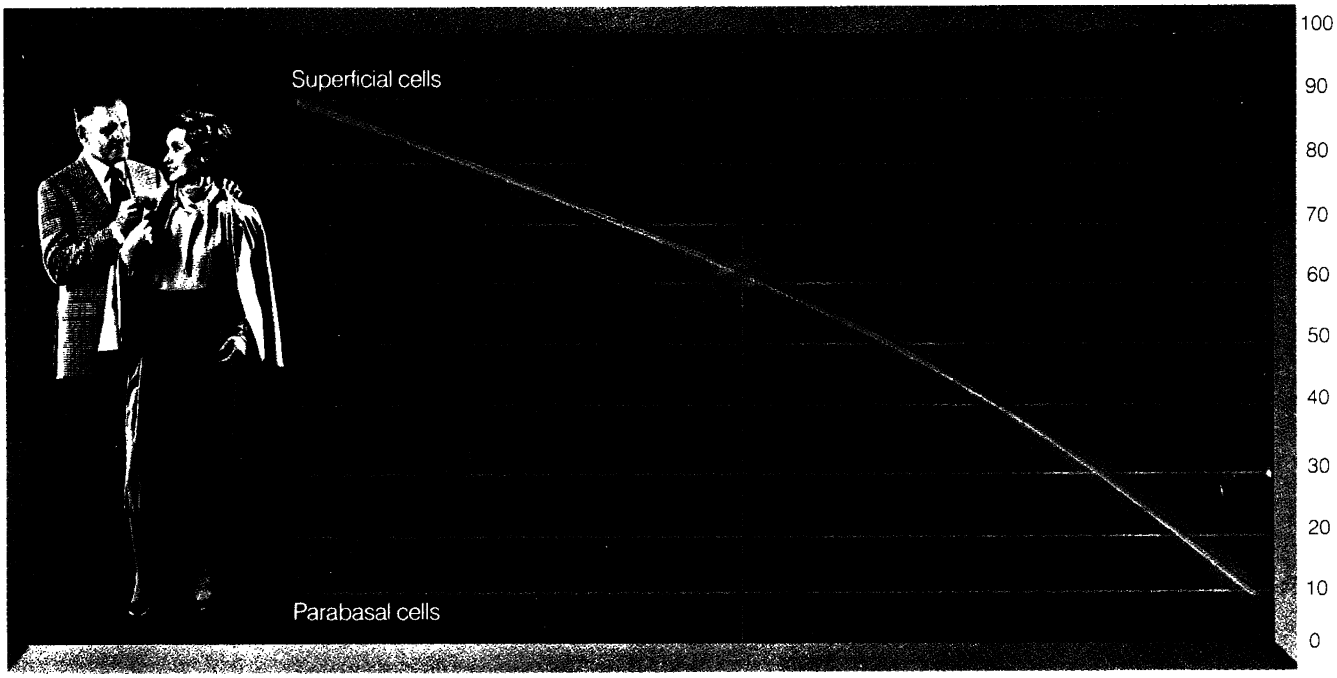
FOR MODERATE TO SEVERE VASOMOTOR SYMPTOMS

PREMARIN®
(CONJUGATED ESTROGENS TABLETS, U.S.P.)

0.3 mg 0.625 mg 1.25 mg 2.5 mg

The appearance of these tablets is a trademark of Ayerst Laboratories.

THE DISTRESSING CONSEQUENCES OF ATROPHIC VAGINITIS



PREMENOPAUSAL CYTOLOGY POSTMENOPAUSAL CYTOLOGY

Estrogen levels—to diagnose estrogen deficiency or monitor replacement therapy—are revealed by cytologic examination of vaginal smears. Since estrogen is essential for their maturation, the predominance of superficial cells is an indicator of high estrogen levels—characteristic of the younger woman. Postmenopausal estrogen depletion is characterized by a corresponding decline in superficial cells and a significant rise in parabasal cells.

THERAPY AS SPECIFIC AS THE PROBLEM

Cytologic examination of vaginal smears can be used as part of the diagnosis of estrogen deficiency.[4] Topical application of PREMARIN® (Conjugated Estrogens, U.S.P.) Vaginal Cream may be appropriate.[2] Therapy is concentrated just where it is needed—in the vaginal environment.

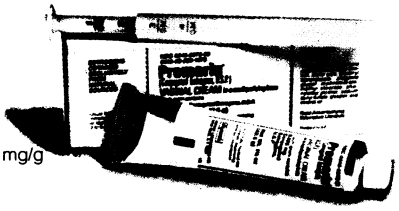
PREMARIN Vaginal Cream has been shown to significantly increase the number of superficial cells in menopausal women within one month.[5] It stimulates epithelial proliferation of the vulva and vagina—returning them to a healthier state in one or two weeks. Symptoms such as dryness, burning, and itching are relieved.[2] Vaginal pH reverts to normal acidity. Normal flora are reestablished, reducing the possibility of local or general infection. Dyspareunia, associated with atrophic vaginitis, is also alleviated.

When vaginal atrophy is the only consequence of estrogen deficiency, PREMARIN Vaginal Cream helps return the vaginal environment to its premenopausal state.

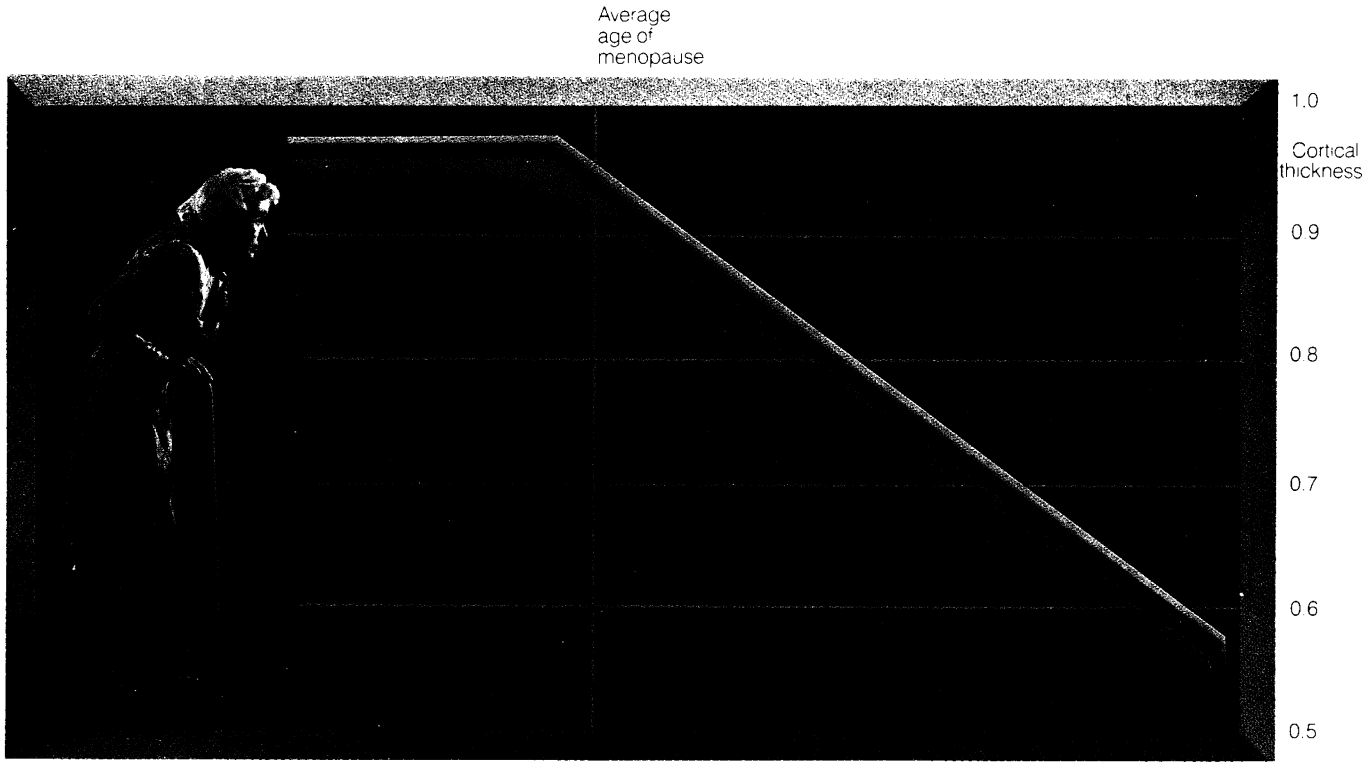
Please see last page for brief summary of prescribing information.

FOR ATROPHIC VAGINITIS

PREMARIN®
(CONJUGATED ESTROGENS, U.S.P.) VAGINAL CREAM



THE DISABLING COURSE OF OSTEOPOROSIS



The graph demonstrates the decrease in cortical thickness that commences just prior to 50 years—the mean menopausal age in women—and accelerates precipitously thereafter. —adapted from Worley, p 204.[6]

THE SOONER TREATMENT BEGINS, THE BETTER

Once osteoporosis is diagnosed, PREMARIN® (Conjugated Estrogens Tablets, U.S.P.) may prove highly beneficial in retarding further bone loss.* PREMARIN treatment should be initiated promptly after osteoporosis is detected to help arrest bone resorption throughout the skeleton, including long bones, pelvic bones, and vertebrae—which are particularly susceptible to trauma. Along with PREMARIN, evaluation of diet, calcium intake, and physical exercise is recommended.

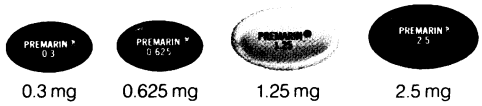
Watching for early warning signals of osteoporosis in high-risk patients is vital. These individuals can be identified by a composite of certain characteristics: white race, slender, slight build, premature or surgical menopause, sedentary life-style, family history of the disease, as well as high caffeine intake, cigarette smoking, and alcoholism.

Osteoporosis affects one of four postmenopausal women.[7] Based on 1980 census data which reports that 23.3 million women were in the 45–64 year age group, over 5 million women may suffer from this condition.[8] Once the damage is done, it is too late to restore bone that has been lost. That's why scientific literature stresses the need for early detection.[9] After osteoporosis is confirmed, early intervention with PREMARIN may be the best course to take.

Please see last page for brief summary of prescribing information.

FOR POSTMENOPAUSAL OSTEOPOROSIS*

PREMARIN® (CONJUGATED ESTROGENS TABLETS, U.S.P.)



0.3 mg 0.625 mg 1.25 mg 2.5 mg

The appearance of these tablets is a trademark of Ayerst Laboratories.

*Conjugated Estrogens Tablets have been evaluated as probably effective for treating postmenopausal osteoporosis.

BRIEF SUMMARY *(FOR FULL PRESCRIBING INFORMATION AND PATIENT INFORMATION, SEE PACKAGE CIRCULAR)*

PREMARIN® Brand of Conjugated Estrogens Tablets, U.S.P.

PREMARIN® Brand of Conjugated Estrogens, U.S.P. Vaginal Cream in a nonliquefying base

1. ESTROGENS HAVE BEEN REPORTED TO INCREASE THE RISK OF ENDOMETRIAL CARCINOMA.

Three independent case control studies have reported an increased risk of endometrial cancer in postmenopausal women exposed to exogenous estrogens for more than one year. This risk was independent of the other known risk factors for endometrial cancer. These studies are further supported by the finding that incidence rates of endometrial cancer have increased sharply since 1969 in eight different areas of the United States with population-based cancer reporting systems, an increase which may be related to the rapidly expanding use of estrogens during the last decade. The three case control studies reported that the risk of endometrial cancer in estrogen users was about 4.5 to 13.9 times greater than in nonusers. The risk appears to depend on both duration of treatment and on estrogen dose. In view of these findings, when estrogens are used for the treatment of menopausal symptoms, the lowest dose that will control symptoms should be utilized and medication should be discontinued as soon as possible. When prolonged treatment is medically indicated, the patient should be reassessed on at least a semiannual basis to determine the need for continued therapy. Although the evidence must be considered preliminary, one study suggests that cyclic administration of low doses of estrogen may carry less risk than continuous administration; it therefore appears prudent to utilize such a regimen. Close clinical surveillance of all women taking estrogens is important. In all cases of undiagnosed persistent or recurring abnormal vaginal bleeding, adequate diagnostic measures should be undertaken to rule out malignancy. There is no evidence at present that "natural" estrogens are more or less hazardous than "synthetic" estrogens at equiestrogenic doses.

2. ESTROGENS SHOULD NOT BE USED DURING PREGNANCY.

The use of female sex hormones, both estrogens and progestogens, during early pregnancy may seriously damage the offspring. It has been shown that females exposed in utero to diethylstilbestrol, a non-steroidal estrogen, have an increased risk of developing in later life a form of vaginal or cervical cancer that is ordinarily extremely rare. This risk has been estimated as not greater than 4 per 1000 exposures. Furthermore, a high percentage of such exposed women (from 30 to 90 percent) have been found to have vaginal adenosis, epithelial changes of the vagina and cervix. Although these changes are histologically benign, it is not known whether they are precursors of malignancy. Although similar data are not available with the use of other estrogens, it cannot be presumed they would not induce similar changes. Several reports suggest an association between intrauterine exposure to female sex hormones and congenital anomalies, including congenital heart defects and limb reduction defects. One case control study estimated a 4.7-fold increased risk of limb reduction defects in infants exposed in utero to sex hormones (oral contraceptives, hormone withdrawal tests for pregnancy, or attempted treatment for threatened abortion). Some of these exposures were very short and involved only a few days of treatment. The data suggest that the risk of limb reduction defects in exposed fetuses is somewhat less than 1 per 1000. In the past, female sex hormones have been used during pregnancy in an attempt to treat threatened or habitual abortion. There is considerable evidence that estrogens are ineffective for these indications, and there is no evidence from well controlled studies that progestogens are effective for these uses. If PREMARIN is used during pregnancy, or if the patient becomes pregnant while taking this drug, she should be apprised of the potential risks to the fetus, and the advisability of pregnancy continuation.

DESCRIPTION: PREMARIN (Conjugated Estrogens, U.S.P.) contains a mixture of estrogens, obtained exclusively from natural sources, blended to represent the average composition of material derived from pregnant mares' urine. It contains estrone, equilin, and 17α-dihydroequilin, together with smaller amounts of 17α-estradiol, equilenin, and 17α-dihydroequilenin as salts of their sulfate esters.

INDICATIONS: Based on a review of PREMARIN Tablets by the National Academy of Sciences—National Research Council and/or other information, FDA has classified the indications for use as follows:

Effective: 1. Moderate to severe vasomotor symptoms associated with the menopause. (There is no evidence that estrogens are effective for nervous symptoms or depression without associated vasomotor symptoms, and they should not be used to treat such conditions.)

2. Atrophic vaginitis
3. Kraurosis vulvae
4. Female hypogonadism
5. Female castration
6. Primary ovarian failure
7. Breast cancer (for palliation only) in appropriately selected women and men with metastatic disease.
8. Prostatic carcinoma—palliative therapy of advanced disease.
9. Postpartum breast engorgement—Although estrogens have been widely used for the prevention of postpartum breast engorgement, controlled studies have demonstrated that the incidence of significant painful engorgement in patients not receiving such hormonal therapy is low and usually responsive to appropriate analgesic or other supportive therapy. Consequently, the benefit to be derived from estrogen therapy for this indication must be carefully weighed against the potential increased risk of puerperal thromboembolism associated with the use of large doses of estrogens.

PREMARIN HAS NOT BEEN SHOWN TO BE EFFECTIVE FOR ANY PURPOSE DURING PREGNANCY AND ITS USE MAY CAUSE SEVERE HARM TO THE FETUS (SEE BOXED WARNING).

"Probably" effective: For estrogen deficiency-induced osteoporosis, and only when used in conjunction with other important therapeutic measures such as diet, calcium, physiotherapy, and good general health-promoting measures. Final classification of this indication requires further investigation.

INDICATIONS: PREMARIN (Conjugated Estrogens, U.S.P.) Vaginal Cream is indicated in the treatment of atrophic vaginitis and kraurosis vulvae. PREMARIN Vaginal Cream HAS NOT BEEN SHOWN TO BE EFFECTIVE FOR ANY PURPOSE DURING PREGNANCY AND ITS USE MAY CAUSE SEVERE HARM TO THE FETUS (SEE BOXED WARNING).

CONTRAINDICATIONS: Estrogens should not be used in women (or men) with any of the following conditions: 1. Known or suspected cancer of the breast except in appropriately selected patients being treated for metastatic disease. 2. Known or suspected estrogen-dependent neoplasia. 3. Known or suspected pregnancy (See Boxed Warning). 4. Undiagnosed abnormal genital bleeding. 5. Active thrombophlebitis or thromboembolic disorders. 6. A past history of thrombophlebitis, thrombosis, or thromboembolic disorders associated with previous estrogen use (except when used in treatment of breast or prostatic malignancy).

WARNINGS: Long term continuous administration of natural and synthetic estrogens in certain animal species increases the frequency of carcinomas of the breast, cervix, vagina, and liver. There are now reports that estrogens increase the risk of carcinoma of the endometrium in humans. (See Boxed Warning.) At the present time there is no satisfactory evidence that estrogens given to postmenopausal women increase the risk of cancer of the breast, although a recent study has raised this possibility. There is a need for caution in prescribing estrogens for women with a strong family history of breast cancer or who have breast nodules, fibrocystic disease, or abnormal mammograms. A recent study has reported a 2- to 3-fold increase in the risk of surgically confirmed gallbladder disease in women receiving postmenopausal estrogens.

Adverse effects of oral contraceptives may be expected at the larger doses of estrogen used to treat prostatic or breast cancer or postpartum breast engorgement; it has been shown that there is an increased risk of thrombosis in men receiving estrogens for prostatic cancer and women for postpartum breast engorgement. Users of oral contraceptives have an increased risk of diseases, such as thrombophlebitis, pulmonary embolism, stroke, and myocardial infarction. Cases of retinal thrombosis, mesenteric thrombosis, and optic neuritis have been reported in oral contraceptive users. An increased risk of postsurgery thromboembolic complications has also been reported in users of oral contraceptives. If feasible, estrogen should be discontinued at least 4 weeks before surgery of the type associated with an increased risk of thromboembolism, or during periods of prolonged immobilization. Estrogens should not be used in persons with active thrombophlebitis, thromboembolic disorders, or in persons with a history of such disorders in association with estrogen use. They should be used with caution in patients with cerebral vascular or coronary artery disease. Large doses (5 mg conjugated estrogens per day), comparable to those used to treat cancer of the prostate and breast have been shown to increase the risk of nonfatal myocardial infarction, pulmonary embolism and thrombophlebitis. When doses of this size are used, any of the thromboembolic and thrombotic adverse effects should be considered a clear risk.

Benign hepatic adenomas should be considered in estrogen users having abdominal pain and tenderness, abdominal mass, or hypovolemic shock. Hepatocellular carcinoma has been reported in women taking estrogen-containing oral contraceptives. Increased blood pressure may occur with use of estrogens in the menopause and blood pressure should be monitored with estrogen use. A worsening of glucose tolerance has been observed in patients on estrogen-containing oral contraceptives. For this reason, diabetic patients should be carefully observed. Estrogens may lead to severe hypercalcemia in patients with breast cancer and bone metastases.

PRECAUTIONS: Physical examination and a complete medical and family history should be taken prior to the initiation of any estrogen therapy with special reference to blood pressure, breasts, abdomen, and pelvic organs, and should include a Papanicolau smear. As a general rule, estrogen should not be prescribed for longer than one year without another physical examination being performed. Conditions influenced by fluid retention such as asthma, epilepsy, migraine, and cardiac or renal dysfunction, require careful observation. Certain patients may develop manifestations of excessive estrogenic stimulation, such as abnormal or excessive uterine bleeding, mastodynia, etc. Oral contraceptives appear to be associated with an increased incidence of mental depression. Patients with a history of depression should be carefully observed. Preexisting uterine leiomyomata may increase in size during estrogen use. The pathologist should be advised of estrogen therapy when relevant specimens are submitted. If jaundice develops in any patient receiving estrogen, the medication should be discontinued while the cause is investigated. Estrogens should be used with care in patients with impaired liver function, renal insufficiency, metabolic bone diseases associated with hypercalcemia, or in young patients in whom bone growth is not complete.

The following changes may be expected with larger doses of estrogen:

a. Increased sulfobromophthalein retention.

b. Increased prothrombin and factors VII, VIII, IX, and X; decreased antithrombin 3; increased norepinephrine-induced platelet aggregability.

c. Increased thyroid binding globulin (TBG) leading to increased circulating total thyroid hormone, as measured by PBI, T4 by column, or T4 by radioimmunoassay. Free T3 resin uptake is decreased, reflecting the elevated TBG; free T4 concentration is unaltered.

d. Impaired glucose tolerance.

e. Decreased pregnanediol excretion.

f. Reduced response to metyrapone test.

g. Reduced serum folate concentration.

h. Increased serum triglyceride and phospholipid concentration.

As a general principle, the administration of any drug to nursing mothers should be done only when clearly necessary since many drugs are excreted in human milk.

ADVERSE REACTIONS: The following have been reported with estrogenic therapy, including oral contraceptives: breakthrough bleeding, spotting, change in menstrual flow; dysmenorrhea; premenstrual-like syndrome; amenorrhea during and after treatment; increase in size of uterine fibromyomata; vaginal candidiasis, change in cervical erosion and in degree of cervical secretion; cystitis-like syndrome; tenderness, enlargement, secretion (of breasts); nausea, vomiting, abdominal cramps, bloating; cholestatic jaundice; chloasma or melasma which may persist when drug is discontinued; erythema multiforme; erythema nodosum; hemorrhagic eruption; loss of scalp hair; hirsutism; steepening of corneal curvature; intolerance to contact lenses; headache, migraine, dizziness, mental depression, chorea; increase or decrease in weight; reduced carbohydrate tolerance; aggravation of porphyria; edema; changes in libido.

ACUTE OVERDOSAGE: May cause nausea, and withdrawal bleeding may occur in females.

DOSAGE AND ADMINISTRATION:

PREMARIN® Brand of Conjugated Estrogens Tablets, U.S.P.

1. *Given cyclically for short-term use only.* For treatment of moderate to severe *vasomotor* symptoms, atrophic vaginitis, or kraurosis vulvae associated with the menopause (0.3 to 1.25 mg or more daily).

The lowest dose that will control symptoms should be chosen and medication should be discontinued as promptly as possible.

Administration should be cyclic (*e.g.*, three weeks on and one week off).

Attempts to discontinue or taper medication should be made at three to six month intervals.

2. *Given cyclically:* Female hypogonadism. Female castration. Primary ovarian failure. Osteoporosis.

Female hypogonadism—2.5 to 7.5 mg daily, in divided doses for 20 days, followed by a rest period of 10 days' duration. If bleeding does not occur by the end of this period, the same dosage schedule is repeated. The number of courses of estrogen therapy necessary to produce bleeding may vary depending on the responsiveness of the endometrium.

If bleeding occurs before the end of the 10 day period, begin a 20 day estrogen-progestin cyclic regimen with PREMARIN (Conjugated Estrogens Tablets, U.S.P.), 2.5 to 7.5 mg daily in divided doses, for 20 days. During the last five days of estrogen therapy, give an oral progestin. If bleeding occurs before this regimen is concluded, therapy is discontinued and may be resumed on the fifth day of bleeding.

Female castration and primary ovarian failure—1.25 mg daily, cyclically. Adjust upward or downward according to response of the patient. For maintenance, adjust dosage to lowest level that will provide effective control.

Osteoporosis (to retard progression)—1.25 mg daily, cyclically.

3. *Given for a few days:* Prevention of postpartum breast engorgement—3.75 mg every four hours for five doses, or 1.25 mg every four hours for five days.

4. *Given chronically:* Inoperable progressing prostatic cancer—1.25 to 2.5 mg three times daily.

Inoperable progressing breast cancer in appropriately selected men and postmenopausal women—10 mg three times daily for a period of at least three months.

Patients with an intact uterus should be monitored for signs of endometrial cancer and appropriate measures taken to rule out malignancy in the event of persistent or recurring abnormal vaginal bleeding.

PREMARIN® Brand of Conjugated Estrogens, U.S.P. Vaginal Cream

Given cyclically for short-term use only. For treatment of atrophic vaginitis or kraurosis vulvae.

The lowest dose that will control symptoms should be chosen and medication should be discontinued as promptly as possible.

Administration should be cyclic (*e.g.*, three weeks on and one week off).

Attempts to discontinue or taper medication should be made at three to six month intervals.

Usual dosage range: 2 to 4 g daily, intravaginally or topically, depending on the severity of the condition.

Treated patients with an intact uterus should be monitored closely for signs of endometrial cancer and appropriate diagnostic measures should be taken to rule out malignancy in the event of persistent or recurring abnormal vaginal bleeding.

HOW SUPPLIED: PREMARIN (Conjugated Estrogens Tablets, U.S.P.) No. 865—Each *purple* tablet contains 2.5 mg in bottles of 100 and 1,000. No. 866—Each *yellow* tablet contains 1.25 mg in bottles of 100 and 1,000. Also in unit dose package of 100. No. 867—Each *red* tablet contains 0.625 mg in bottles of 100 and 1,000. Also in unit dose package of 100. No. 868—Each *green* tablet contains 0.3 mg in bottles of 100 and 1,000.

PREMARIN (Conjugated Estrogens, U.S.P.) Vaginal Cream—No. 872—Each gram contains 0.625 mg Conjugated Estrogens, U.S.P. (Also contains cetyl esters wax, cetyl alcohol, white wax, glyceryl monostearate, propylene glycol monostearate, methyl stearate, phenylethyl alcohol, sodium lauryl sulfate, glycerin, and mineral oil.)

Combination package: Each contains Net Wt. 1½ oz. (42.5 g) tube with one calibrated plastic applicator.

Also Available—Refill package: Each contains Net Wt. 1½ oz. (42.5 g) tube.

REFERENCES: 1. Erlik Y, Tataryn IV, Meldrum DR, et al: Association of waking episodes with menopausal hot flushes. *JAMA* 1981;245:1741-1744. 2. Judd HL, Meldrum DR, Deftos LJ, et al: Estrogen replacement therapy: Indications and complications. *Ann Intern Med* 1983;98:195-205. 3. Estrogen replacement therapy. *ACOG Tech Bull*, June 1983, pp 1-5. 4. Ayers LJ: The maturation index: A test for estrogen deficiency. *Female Patient* 1982;7:32-36. 5. Semmens JP, Wagner G: Estrogen deprivation and vaginal function in postmenopausal women. *JAMA* 1982;248:445-448. 6. Worley RJ: Age, estrogen, and bone density. *Clin Obstet Gynecol* 1981;24:203-218. 7. Gordan GS, Picchi J, Roof BS, et al: Postmenopausal osteoporosis. *Am Fam Physician* 1973;8:74-83. 8. US Bureau of the Census, *Statistical Abstract of the United States* 1982-83, ed. 103. Washington, DC, US Dept of Commerce, 1982, p 25. 9. Mallette LE: Osteoporosis: Approaching treatment with optimism. *Postgrad Med* 1982;72:271-278.

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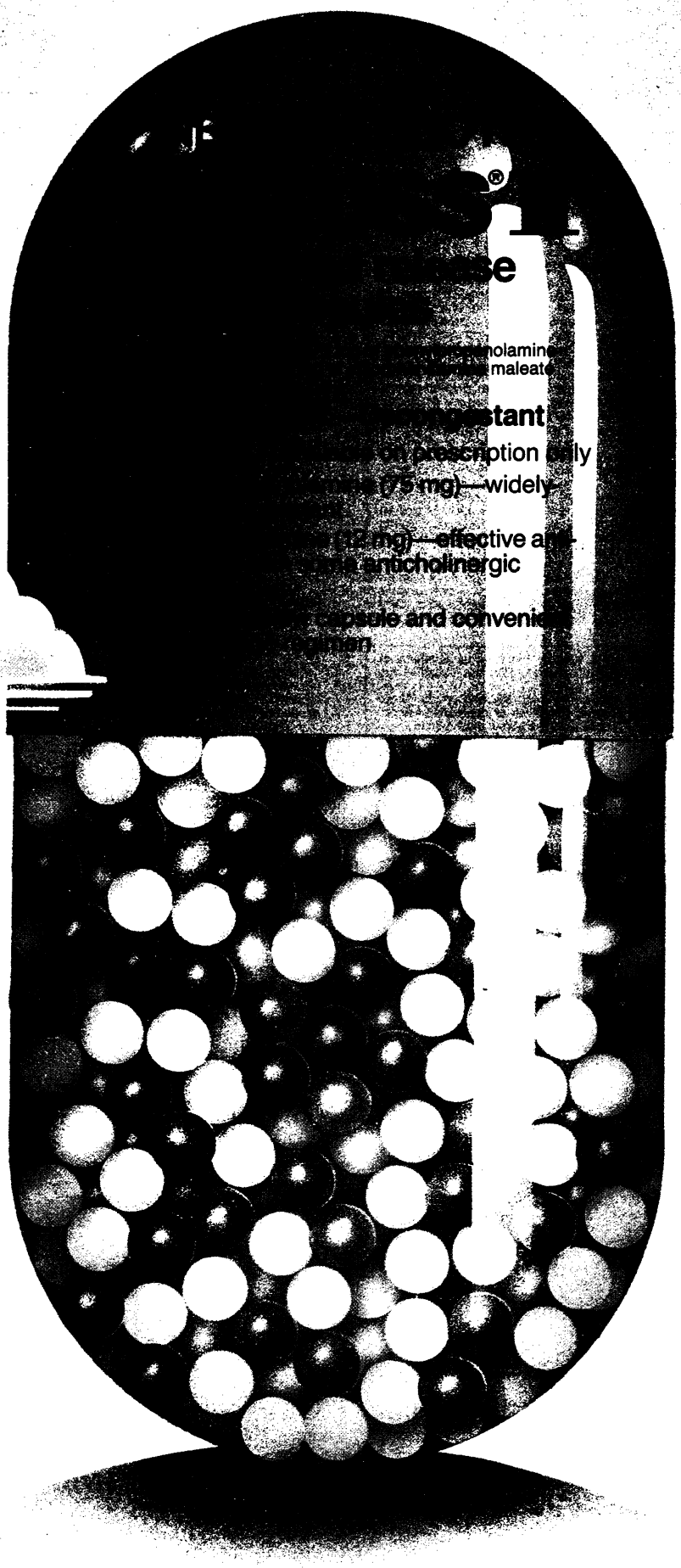

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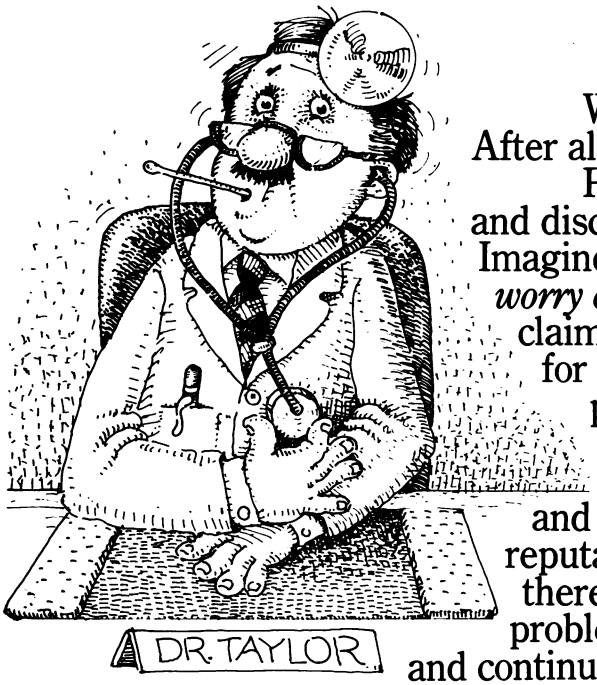

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Please be assured that we won't introduce new medical management procedures and then bid you a fast farewell. We've built a reputation for outstanding service; we'll always be there to help. Our method is to diagnose your problems and then offer consultations, prescriptions and continual support to solve them.

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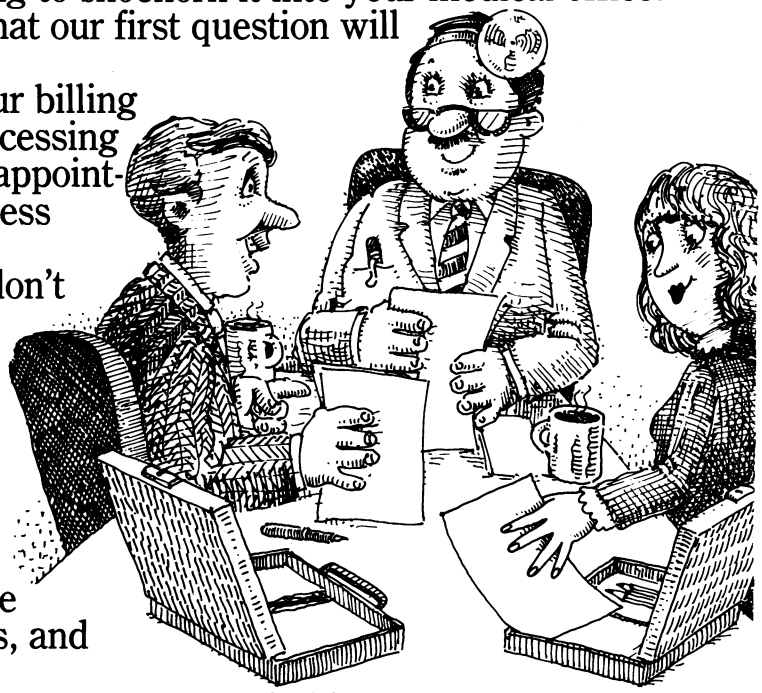

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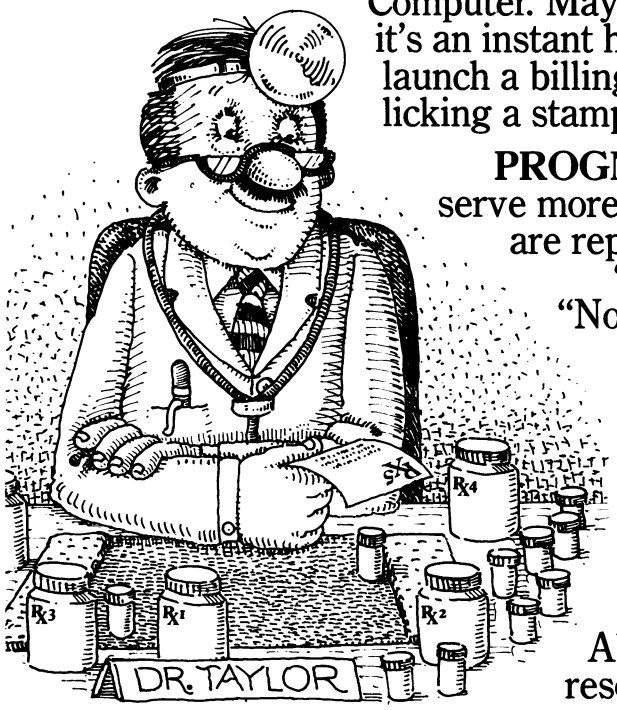

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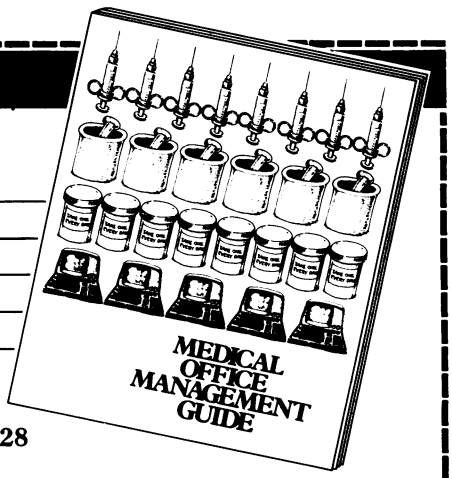

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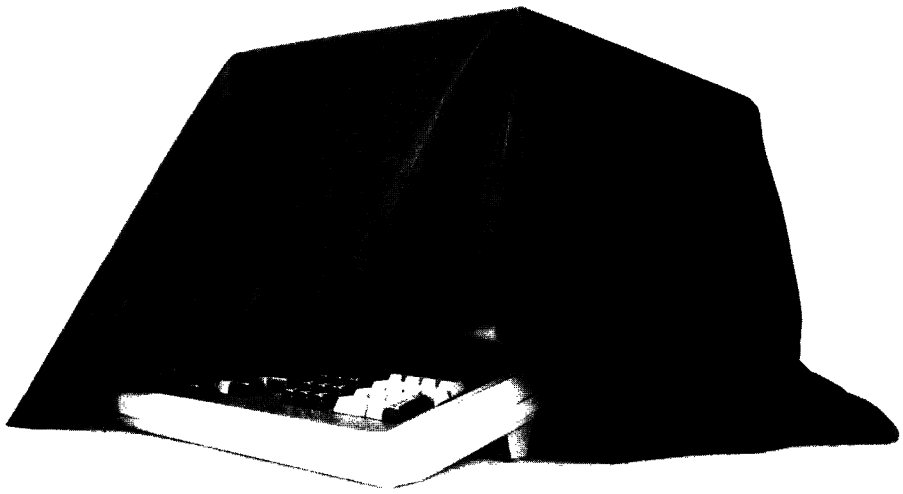

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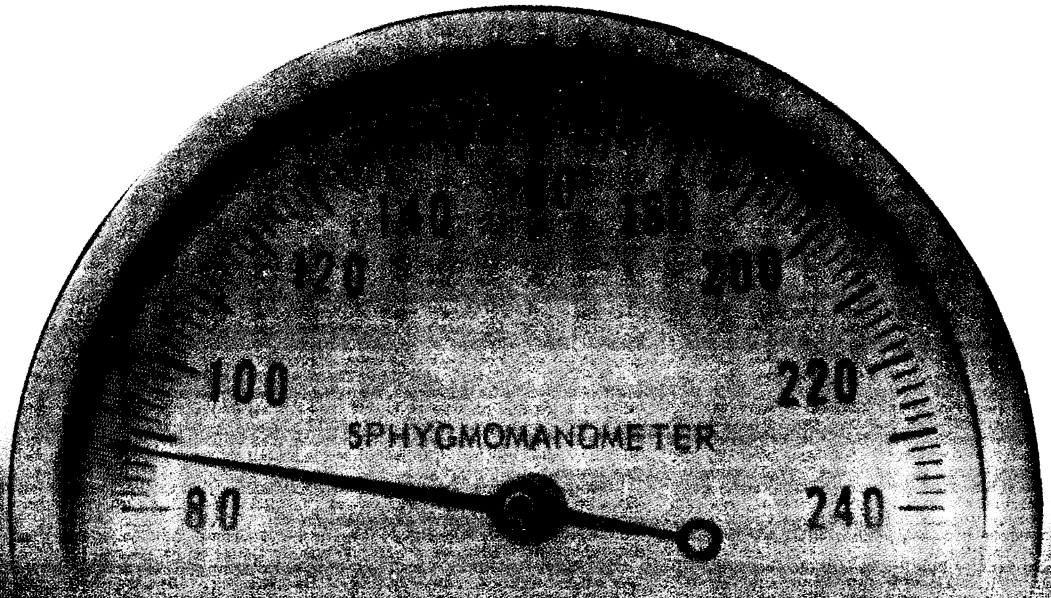

Start with 80 mg once daily... Dosage may be increased to 120 mg or 160 mg once daily as needed to achieve additional control. Please see next page for further details and brief summary of prescribing information.

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Just once each day for initial therapy in HYPERTENSION.

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(PROPRANOLOL HCl) LONG ACTING CAPSULES

80 mg 120 mg 160 mg*

BRIEF SUMMARY *(FOR FULL PRESCRIBING INFORMATION, SEE PACKAGE CIRCULAR.)*
INDERAL® LA brand of propranolol hydrochloride **(Long Acting Capsules)**
DESCRIPTION. Inderal LA is formulated to provide a sustained release of propranolol hydrochloride. Inderal LA is available as 80 mg, 120 mg, and 160 mg capsules.
CLINICAL PHARMACOLOGY. INDERAL is a nonselective beta-adrenergic receptor blocking agent possessing no other autonomic nervous system activity. It specifically competes with beta-adrenergic receptor stimulating agents for available receptor sites. When access to beta-receptor sites is blocked by INDERAL, the chronotropic, inotropic, and vasodilator responses to beta-adrenergic stimulation are decreased proportionately.

INDERAL LA Capsules (80, 120, and 160 mg) release propranolol HCl at a controlled and predictable rate. Peak blood levels following dosing with INDERAL LA occur at about 6 hours and the apparent plasma half-life is about 10 hours. When measured at steady state over a 24-hour period the areas under the propranolol plasma concentration-time curve (AUCs) for the capsules are approximately 60% to 65% of the AUCs for a comparable divided daily dose of INDERAL tablets. The lower AUCs for the capsules are due to greater hepatic metabolism of propranolol, resulting from the slower rate of absorption of propranolol. Over a twenty-four (24) hour period, blood levels are fairly constant for about twelve (12) hours then decline exponentially.

INDERAL LA should not be considered a simple mg for mg substitute for conventional propranolol and the blood levels achieved do not match (are lower than) those of two to four times daily dosing with the same dose. When changing to INDERAL LA from conventional propranolol, a possible need for retitration upwards should be considered especially to maintain effectiveness at the end of the dosing interval. In most clinical settings, however, such as hypertension or angina where there is little correlation between plasma levels and clinical effect, INDERAL LA has been therapeutically equivalent to the same mg dose of conventional INDERAL as assessed by 24-hour effects on blood pressure and on 24-hour exercise responses of heart rate, systolic pressure and rate pressure product. INDERAL LA can provide effective beta blockade for a 24-hour period.

The mechanism of the antihypertensive effect of INDERAL has not been established. Among the factors that may be involved in contributing to the antihypertensive action are (1) decreased cardiac output, (2) inhibition of renin release by the kidneys, and (3) diminution of tonic sympathetic nerve outflow from vasomotor centers in the brain. Although total peripheral resistance may increase initially, it readjusts to or below the pretreatment level with chronic use. Effects on plasma volume appear to be minor and somewhat variable. INDERAL has been shown to cause a small increase in serum potassi[illegible] concentration when use[illegible] the treatment of hypertensive patients.

In angina pectoris, propranolol generally reduces th[illegible]n re[illegible]t any given level of effort by blocking the catecholamine-[illegible]d inc[illegible] in the he[illegible] rate, systolic blood pressure, and the velocity and extent of [illegible]rdial [illegible] Pro[illegible]nolol may increase oxygen requirements by increasing left [illegible]lar fi[illegible] length, [illegible]stolic pressure and systolic ejection period. The net phy[illegible]kade is usually advantageous and is manifested duri[illegible]rcise [illegible] of pa[illegible]nd increased work capacity.

In dosages greater than required for beta blockade, INDERAL also exerts a quinidine-[illegible] or anesthetic-like membrane action which affects th[illegible]c a[illegible]entia[illegible]sig[illegible] cance of the membrane action in the treatment of a[illegible]ythm[illegible] is[illegible]cert[illegible].

The mechanism of the antimigraine effect of pr[illegible]lished. B[illegible]-adrenergic receptors have been demonstrated in [illegible] pial vess[illegible] of th[illegible].

Beta receptor blockade can be useful in cond[illegible]ns in [illegible] bec[illegible] path[illegible]r functional changes, sympathetic activity is detrim[illegible] so situations in which sympathetic stimulation is vital. For example, in patients with severely damaged hearts, adequate ventricular function is maintained by virtue of sympathetic drive which should be preserved. In the presence of AV block, greater than first degree, beta blockade may prevent the necessary facilitating effect of sympathetic activity on conduction. Beta blockade results in bronchial constriction by interfering with adrenergic bronchodilator activity which should be preserved in patients subject to bronchospasm.

Propranolol is not significantly dialyzable.

INDICATIONS AND USAGE. Hypertension: INDERAL LA is indicated in the management of hypertension; it may be used alone or used in combination with other antihypertensive agents, particularly a thiazide diuretic. INDERAL LA is not indicated in the management of hypertensive emergencies.

Angina Pectoris Due to Coronary Atherosclerosis: INDERAL LA is indicated for the long-term management of patients with angina pectoris.

Migraine: INDERAL LA is indicated for the prophylaxis of common migraine headache. The efficacy of propranolol in the treatment of a migraine attack that has started has not been established and propranolol is not indicated for such use.

Hypertrophic Subaortic Stenosis: INDERAL LA is useful in the management of hypertrophic subaortic stenosis, especially for treatment of exertional or other stress-induced angina, palpitations, and syncope. INDERAL LA also improves exercise performance. The effectiveness of propranolol hydrochloride in this disease appears to be due to a reduction of the elevated outflow pressure gradient which is exacerbated by beta-receptor stimulation. Clinical improvement may be temporary.

CONTRAINDICATIONS. INDERAL is contraindicated in 1) cardiogenic shock; 2) sinus bradycardia and greater than first degree block; 3) bronchial asthma; 4) congestive heart failure (see WARNINGS) unless the failure is secondary to a tachyarrhythmia treatable with INDERAL.

WARNINGS. CARDIAC FAILURE: Sympathetic stimulation may be a vital component supporting circulatory function in patients with congestive heart failure, and its inhibition by beta blockade may precipitate more severe failure. Although beta blockers should be avoided in overt congestive heart failure, if necessary, they can be used with close follow-up in patients with a history of failure who are well compensated and are receiving digitalis and diuretics. Beta-adrenergic blocking agents do not abolish the inotropic action of digitalis on heart muscle.

IN PATIENTS WITHOUT A HISTORY OF HEART FAILURE, continued use of beta blockers can, in some cases, lead to cardiac failure. Therefore, at the first sign or symptom of heart failure, the patient should be digitalized and/or treated with diuretics, and the response observed closely, or INDERAL should be discontinued (gradually, if possible).

> IN PATIENTS WITH ANGINA PECTORIS, there have been reports of exacerbation of angina and, in some cases, myocardial infarction, following abrupt discontinuance of INDERAL therapy. Therefore, when discontinuance of INDERAL is planned the dosage should be gradually reduced over at least a few weeks, and the patient should be cautioned against interruption or cessation of therapy without the physician's advice. If INDERAL therapy is interrupted and exacerbation of angina occurs, it usually is advisable to reinstitute INDERAL therapy and take other measures appropriate for the management of unstable angina pectoris. Since coronary artery disease may be unrecognized, it may be prudent to follow the above advice in patients considered at risk of having occult atherosclerotic heart disease who are given propranolol for other indications.

Nonallergic Bronchospasm (e.g., chronic bronchitis, emphysema)—PATIENTS WITH BRONCHOSPASTIC DISEASES SHOULD IN GENERAL NOT RECEIVE BETA BLOCKERS. INDERAL should be administered with caution since it may block bronchodilation produced by endogenous and exogenous catecholamine stimulation of beta receptors.

MAJOR SURGERY: The necessity or desirability of withdrawal of beta-blocking therapy prior to major surgery is controversial. It should be noted, however, that the impaired ability of the heart to respond to reflex adrenergic stimuli may augment the risks of general anesthesia and surgical procedures.

INDERAL (propranolol HCl), like other beta blockers, is a competitive inhibitor of beta-receptor agonists and its effects can be reversed by administration of such agents, e.g., dobutamine or isoproterenol. However, such patients may be subject to protracted severe hypotension. Difficulty in starting and maintaining the heartbeat has also been reported with beta blockers.

DIABETES AND HYPOGLYCEMIA: Beta-adrenergic blockade may prevent the appearance of certain premonitory signs and symptoms (pulse rate and pressure changes) of acute hypoglycemia in labile insulin-dependent diabetes. In these patients, it may be more difficult to adjust the dosage of insulin.

THYROTOXICOSIS: Beta blockade may mask certain clinical signs of hyperthyroidism. Therefore, abrupt withdrawal of propranolol may be followed by an exacerbation of symptoms of hyperthyroidism, including thyroid storm. Propranolol does not distort thyroid function tests.

IN PATIENTS WITH WOLFF-PARKINSON-WHITE SYNDROME, several cases have been reported in which, after propranolol, the tachycardia was replaced by a severe bradycardia requiring a demand pacemaker. In one case this resulted after an initial dose of 5 mg propranolol.

PRECAUTIONS. *General:* Propranolol should be used with caution in patients with impaired hepatic or renal function. INDERAL is not indicated for the treatment of hypertensive emergencies.

Beta adrenoreceptor blockade can cause reduction of intraocular pressure. Patients should be told that INDERAL may interfere with the glaucoma screening test. Withdrawal may lead to a return of increased intraocular pressure.

Clinical Laboratory Tests: Elevated blood urea levels in patients with severe heart disease, elevated serum transaminase, alkaline phosphatase, lactate dehydrogenase.

DRUG INTERACTIONS: Patients receiving catecholamine-depleting drugs such as reserpine should be closely observed if INDERAL is administered. The added catecholamine-blocking action may produce an excessive reduction of resting sympathetic nervous activity which may result in hypotension, marked bradycardia, vertigo, syncopal attacks, or orthostatic hypotension.

Carcinogenesis, Mutagenesis, Impairment of Fertility: Long-term studies in animals have been conducted to evaluate toxic effects and carcinogenic potential. In 18-month studies in both rats and mice, employing doses up to 150 mg/kg/day, there was no evidence of significant [illegible] elated tumorigenic effects at any of the dosage levels. [illegible]oduc[illegible]dies [illegible]mals [illegible] not show any impairment of fertility that was attrib[illegible] to the [illegible].

[illegible]ncy: [illegible]ncy Cat[illegible]ry C. INDERAL has been shown to be embryotoxic in [illegible] studies at [illegible]er than the maximum recommended human dose. There are no adequate and well-controlled studies in pregnant women. INDERAL should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nursing Mot[illegible]s: INDERAL is excreted in human milk. Caution should be exercised when INDERAL [illegible] to a nursing woman.

Pe[illegible]ric [illegible] ety a[illegible] ctive[illegible]ss in children have not been established.

[illegible]VE[illegible]SE R[illegible]CTIONS. [illegible] adverse effects have been mild and transient and have rarely [illegible]quired [illegible] of [illegible].

C[illegible]iovas[illegible] brady[illegible]dia[illegible] gestive heart failure; intensification of AV block; hypotension[illegible] thr[illegible]urpura; arterial insufficiency, usually of the Raynaud type.

Central Nervous System: [illegible]headedness; mental depression manifested by insomnia, lassitude, weakness, fatigue, reversible mental depression progressing to catatonia; visual disturbances; hallucinations; an acute reversible syndrome characterized by disorientation for time and place, short-term memory loss, emotional lability, slightly clouded sensorium, and decreased performance on neuropsychometrics.

Gastrointestinal: nausea, vomiting, epigastric distress, abdominal cramping, diarrhea, constipation, mesenteric arterial thrombosis, ischemic colitis.

Allergic: pharyngitis and agranulocytosis, erythematous rash, fever combined with aching and sore throat, laryngospasm and respiratory distress.

Respiratory: bronchospasm.

Hematologic: agranulocytosis, nonthrombocytopenic purpura, thrombocytopenic purpura.

Auto-Immune: In extremely rare instances, systemic lupus erythematosus has been reported.

Miscellaneous: alopecia, LE-like reactions, psoriasiform rashes, dry eyes, male impotence, and Peyronie's disease have been reported rarely. Oculomucocutaneous reactions involving the skin, serous membranes and conjunctivae reported for a beta blocker (practolol) have not been associated with propranolol.

DOSAGE AND ADMINISTRATION. INDERAL LA provides propranolol hydrochloride in a sustained-release capsule for administration once daily. If patients are switched from INDERAL tablets to INDERAL LA capsules, care should be taken to assure that the desired therapeutic effect is maintained. INDERAL LA should not be considered a simple mg for mg substitute for INDERAL. INDERAL LA has different kinetics and produces lower blood levels. Retitration may be necessary especially to maintain effectiveness at the end of the 24-hour dosing interval.

HYPERTENSION—*Dosage must be individualized.* The usual initial dosage is 80 mg INDERAL LA once daily, whether used alone or added to a diuretic. The dosage may be increased to 120 mg once daily or higher until adequate blood-pressure control is achieved. The usual maintenance dosage is 120 to 160 mg once daily. In some instances a dosage of 640 mg may be required. The time needed for full hypertensive response to a given dosage is variable and may range from a few days to several weeks.

ANGINA PECTORIS—*Dosage must be individualized.* Starting with 80 mg INDERAL LA once daily, dosage should be gradually increased at three to seven day intervals until optimum response is obtained. Although individual patients may respond at any dosage level, the average optimum dosage appears to be 160 mg once daily. In angina pectoris, the value and safety of dosage exceeding 320 mg per day have not been established.

If treatment is to be discontinued, reduce dosage gradually over a period of a few weeks (see WARNINGS).

MIGRAINE—*Dosage must be individualized.* The initial oral dose is 80 mg INDERAL LA once daily. The usual effective dose range is 160-240 mg once daily. The dosage may be increased gradually to achieve optimum migraine prophylaxis. If a satisfactory response is not obtained within four to six weeks after reaching the maximum dose, INDERAL LA therapy should be discontinued. It may be advisable to withdraw the drug gradually over a period of several weeks.

HYPERTROPHIC SUBAORTIC STENOSIS—80-160 mg INDERAL LA once daily.

PEDIATRIC DOSAGE—At this time the data on the use of the drug in this age group are too limited to permit adequate directions for use.

*The appearance of INDERAL LA capsules is a registered trademark of Ayerst Laboratories.

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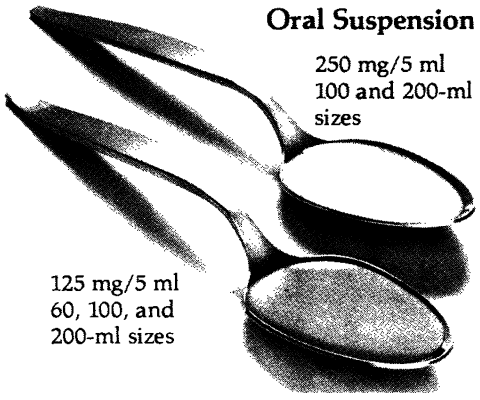

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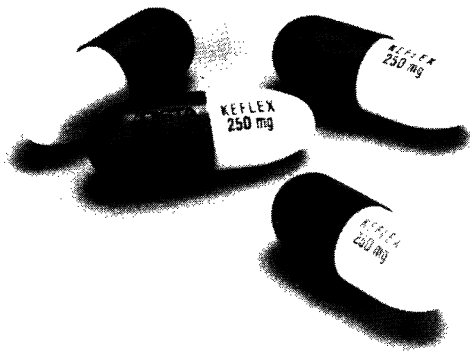

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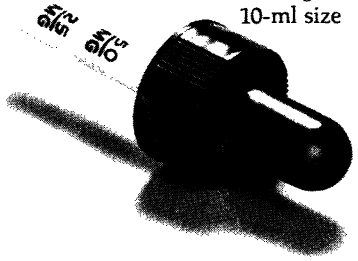

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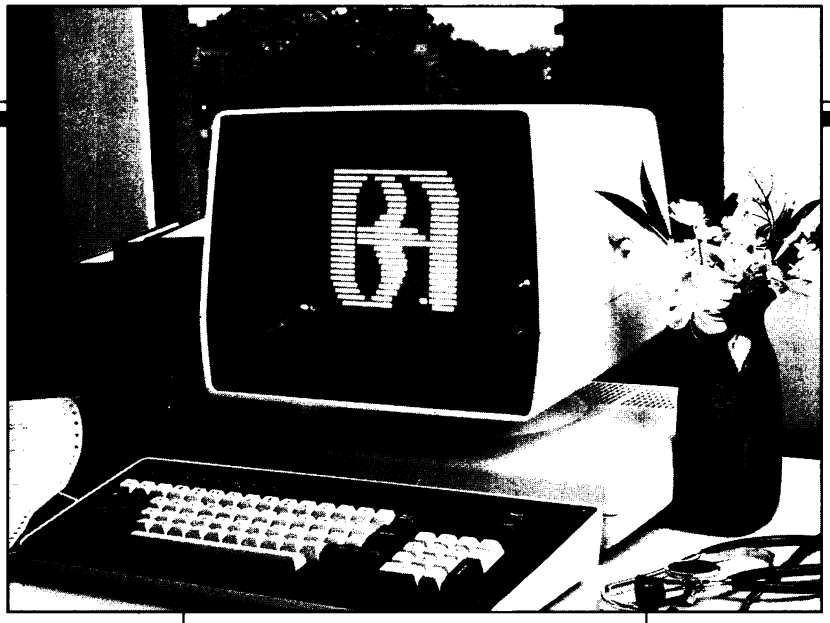

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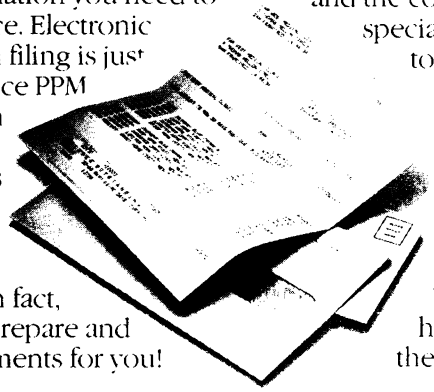

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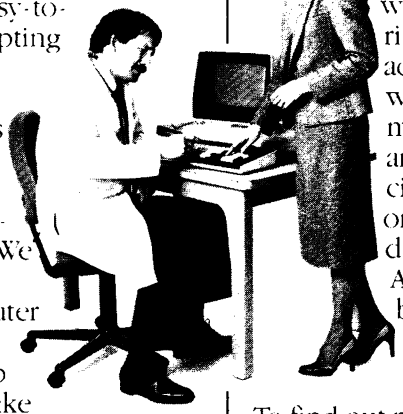

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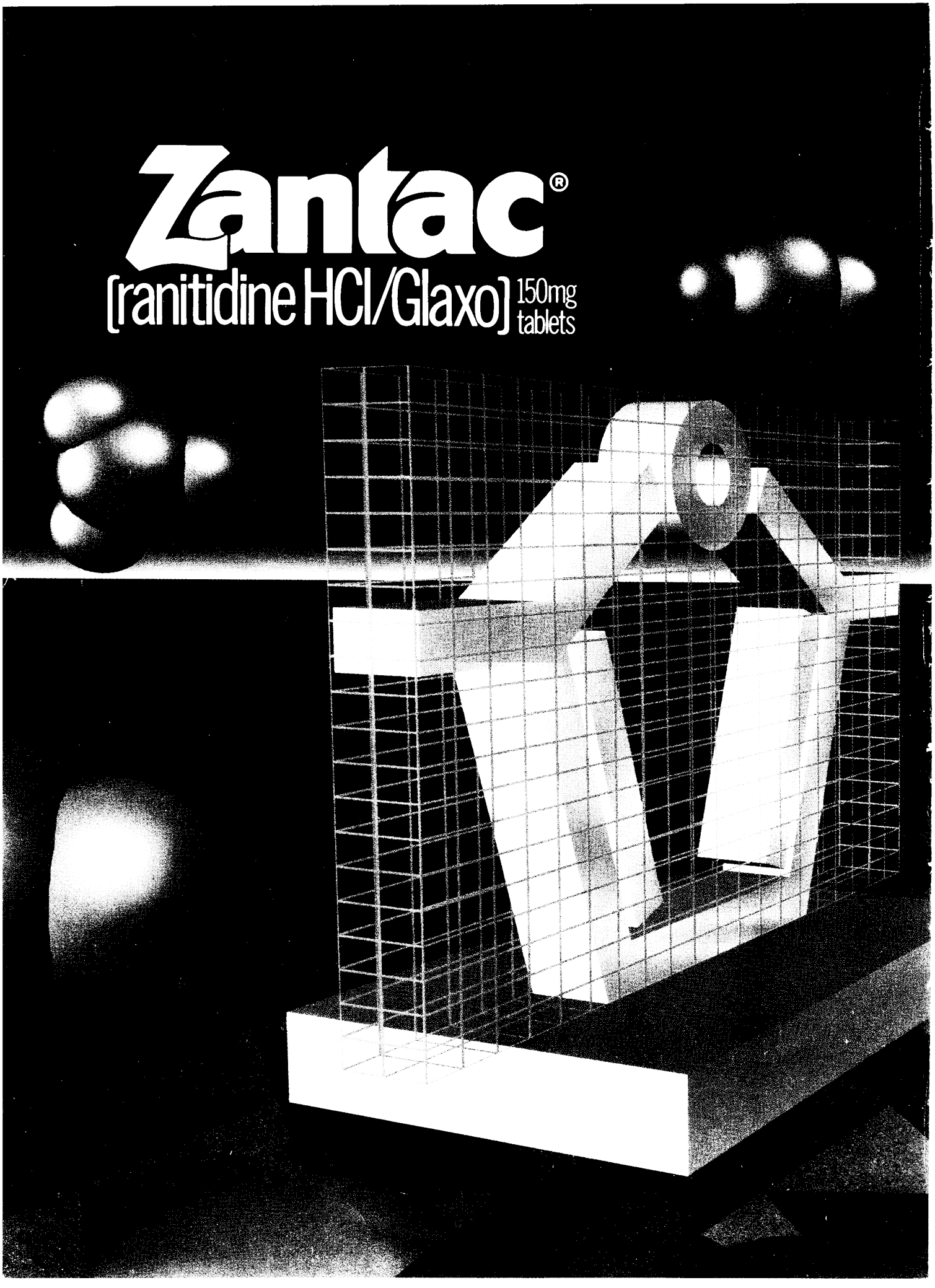
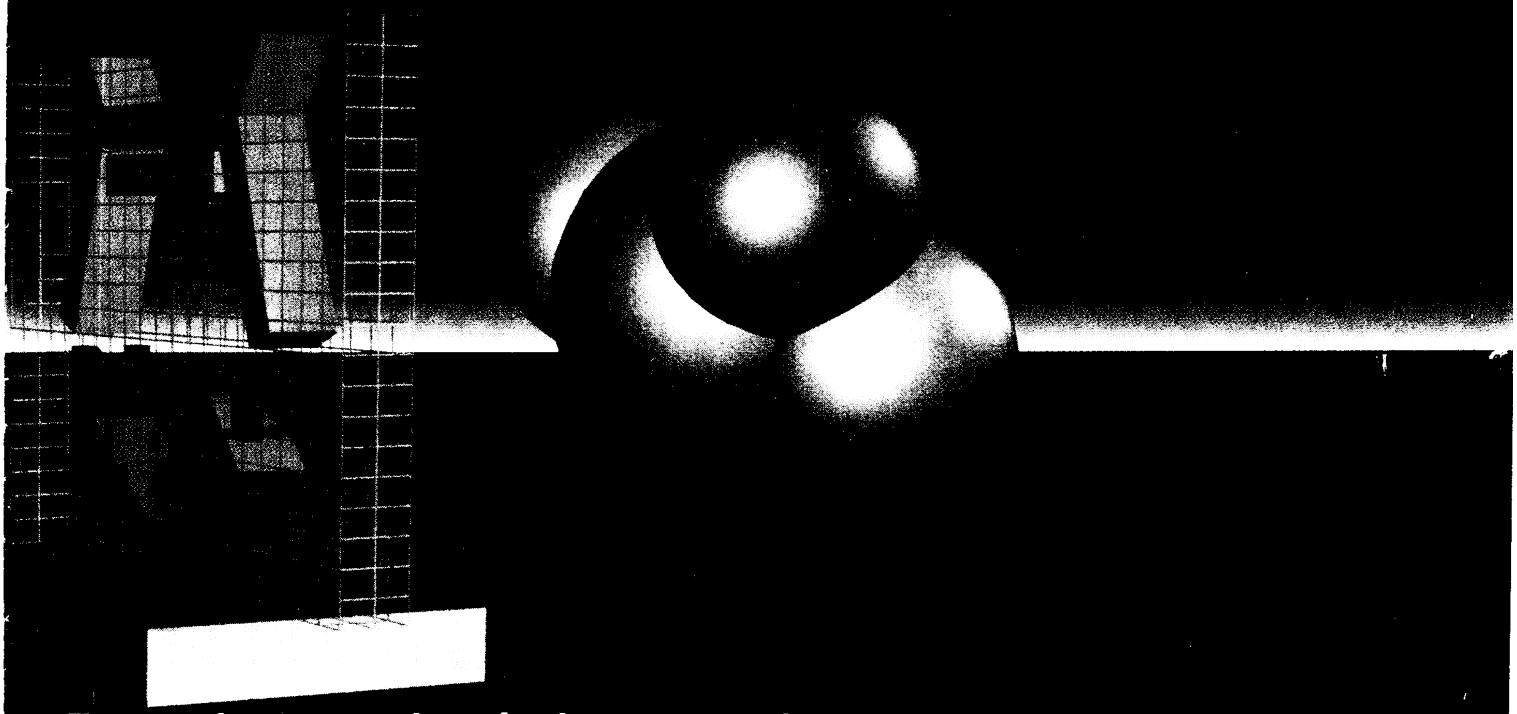

Zantac®
[ranitidine HCl/Glaxo] 150mg tablets

Glaxo ROCHE

Unsurpassed activity in gastric acid inhibition: for active duodenal ulcer and pathological hypersecretory conditions*



Zantac is a new chemical compound

- ☐ Not a histamine-related imidazole—a furan compound.

Zantac offers important patient benefits

- ☐ Single-dose action for up to 12 hours—b.i.d. administration. Four weeks of therapy for most patients with active duodenal ulcer.
- ☐ No interaction with warfarin, theophylline and diazepam.
- ☐ Effective and well tolerated even in pathological hypersecretory conditions.
- ☐ For adverse reactions see complete prescribing information.

*It is not known exactly how much inhibition of gastric acid secretion is required to heal ulcers.

Please see following page for complete prescribing information.

Unsurpassed activity in gastric acid inhibition

Zantac®

[ranitidine HCl/Glaxo] 150mg tablets

DESCRIPTION: The active ingredient in ZANTAC® Tablets, ranitidine hydrochloride, is a histamine H_2 receptor antagonist. Chemically it is N[2-[[[5-[(dimethylamino) methyl]-2-furanyl]methyl]thio]ethyl]-N'-methyl-2-nitro-1, 1-ethenediamine, hydrochloride. It has the following structure:

The empirical formula is $C_{13}H_{22}N_4O_3S \cdot HCl$, representing a molecular weight of 350.87.

Ranitidine hydrochloride is a white to pale yellow granular substance which is soluble in water. It has a slightly bitter taste and sulphur-like odor.

Each tablet for oral administration contains 168 mg of ranitidine hydrochloride, equivalent to 150 mg ranitidine.

CLINICAL PHARMACOLOGY: ZANTAC® (ranitidine hydrochloride) is a competitive, reversible inhibitor of the action of histamine at the histamine H_2 receptors, including receptors on the gastric cells.

ZANTAC does not lower serum Ca^{++} in hypercalcemic states.

ZANTAC is not an anticholinergic agent.

Antisecretory Activity:

1. Effects on acid secretion:

ZANTAC inhibits both daytime and nocturnal basal gastric acid secretion as well as gastric acid secretion stimulated by food, histamine and pentagastrin, as shown in the table below.

Effect of Oral ZANTAC® on Gastric Acid Secretion

	Time After Dose, hrs.	% Inhibition of Gastric Acid Output by Dose, mg			
		75-80	100	150	200
Basal	Up to 4		99	95	
Nocturnal	Up to 13	95	96	92	
Betazole	Up to 3		97	99	
Pentagastrin	Up to 5	58	72	72	80
Meal	Up to 3		73	79	95

It appears that basal, nocturnal and betazole stimulated secretion are most sensitive to inhibition by ZANTAC, responding almost completely to doses of 100 mg or less, while pentagastrin and food stimulated secretion are more difficult to suppress.

2. Effects on other gastrointestinal secretions:

Pepsin: Oral ZANTAC 150 mg did not affect pepsin secretion. Total pepsin output was reduced in proportion to the decrease in volume of gastric juice.

Intrinsic factor: Oral ZANTAC 150 mg had no significant effect on pentagastrin-stimulated intrinsic factor secretion.

Serum gastrin: ZANTAC has little or no effect on fasting or postprandial serum gastrin.

3. Other pharmacological actions:

a. Hepatic blood flow reduced 20%. Significance unknown.
b. Gastric bacterial flora—increase in nitrate-reducing organisms, significance not known.
c. Prolactin—no effect (IV bolus) or less increase than cimetidine.
d. Other pituitary hormones—no effect on serum gonadotropins, TSH, GH. Possible impairment of vasopressin release.
e. No change in cortisol or aldosterone.
f. No effect on count, motility or morphology of sperm, androgen level, estradiol, testosterone.
g. No effect on penile erection, sexual arousal or ejaculation.

4. Pharmacokinetics:

ZANTAC is 50% absorbed after oral administration compared to an IV injection with mean peak levels of 440-545 ng/ml occurring at 2-3 hours after a 150 mg dose. The elimination half-life is 2.5-3 hours.

Absorption of ZANTAC is not significantly impaired by concomitant administration of food or antacids. Propantheline slightly delays and increases peak blood levels of ZANTAC, probably by delaying gastric emptying and transit time.

Serum concentrations necessary to inhibit 50% of stimulated gastric acid secretion are estimated to be 36-94 ng/ml. Following a single oral dose of 150 mg, serum concentrations of ZANTAC are in this range up to 12 hours. However, blood levels bear no consistent relationship to dose or degree of acid inhibition.

The principal route of excretion is the urine, with approximately 30% of the orally administered dose collected in the urine as unchanged drug in 24 hours. Renal clearance is about 410 ml/min, indicating active tubular excretion.

In man, the N-oxide is the principal metabolite in the urine; however this amounts to less than 4% of the dose. Other metabolites are the S-oxide (1%) and the desmethyl ranitidine (1%). The remainder of the administered dose is found in the stool.

The volume of distribution is about 1.4 L/kg. Serum protein binding averages 15%.

Clinical Trials:

Duodenal Ulcer

In a multicenter, double-blind controlled U.S. study of endoscopically diagnosed duodenal ulcers, earlier healing was seen in the ZANTAC®-treated patients as shown below:

	ZANTAC® +		Placebo +	
	Number Entered	Healed/ Evaluable	Number Entered	Healed/ Evaluable
Outpatients				
Week 2	149	54/147 (37%)*	146	29/137 (21%)
Week 4		109/148 (74%)**		68/137 (50%)

*p = 0.0014
**p = 0.0001
+ All patients were permitted prn antacids for relief of pain.

In these studies, ZANTAC-treated patients reported a reduction in both daytime and nocturnal pain, and they also consumed less antacid than the placebo-treated patients.

	Median number of daily doses of antacid	
	Ulcer Healed	Ulcer Not Healed
ZANTAC®	0.06	0.71
Placebo	0.71	1.43

During the clinical trials, some not healed at 4 weeks were rerandomized to either placebo or ranitidine, with the results after 4 weeks shown below.

Not healed on:	Retreated with:	Healed:
Placebo	Placebo	10/21
Placebo	Ranitidine	15/24
Ranitidine	Ranitidine	5/8
Ranitidine	Placebo	8/19

It can be seen that there are trends weakly favoring ranitidine but none of the differences are statistically significant.

Studies have been limited to short-term treatment of acute duodenal ulcer. Patients whose ulcers healed during therapy had recurrences of ulcers at the usual rates. There have been no systematic studies to evaluate whether continued treatment with ZANTAC (ranitidine hydrochloride) alters recurrence rates.

Pathological Hypersecretory Conditions

(such as Zollinger-Ellison Syndrome)

ZANTAC inhibits gastric acid secretion and reduces occurrence of diarrhea, anorexia, and pain in patients with pathological hypersecretion associated with Zollinger-Ellison Syndrome, systemic mastocytosis and other pathological hypersecretory conditions (e.g. post-operative, "short gut" syndrome, idiopathic). Use of ZANTAC was followed by healing of ulcers in 8 of 19 (42%) patients who were intractable to previous therapy.

INDICATIONS AND USAGE:

ZANTAC® (ranitidine hydrochloride) is indicated in:

1. Short-term treatment of active duodenal ulcer. Most patients heal within 4 weeks and the usefulness of further treatment has not been demonstrated. Studies available to date have not assessed the safety of ranitidine in uncomplicated duodenal ulcer for periods of more than 8 weeks.

2. The treatment of pathological hypersecretory conditions (e.g., Zollinger-Ellison Syndrome and systemic mastocytosis).

In active duodenal ulcer and hypersecretory states, concomitant antacids should be given as needed for relief of pain.

CONTRAINDICATIONS: There are no known contraindications to the use of ZANTAC® (ranitidine hydrochloride).

PRECAUTIONS:

General

1. Symptomatic response to ZANTAC® therapy does not preclude the presence of gastric malignancy.

2. Since ZANTAC is excreted primarily by the kidney, dosage should be adjusted in patients with impaired renal function (see Dosage and Administration). Caution should be observed in patients with hepatic dysfunction; ZANTAC is metabolized in the liver and, at present, the effects of hepatic disease on the metabolism of ZANTAC is unknown.

Laboratory Tests

False positive tests for urine protein with Multistix® may occur during ZANTAC therapy and therefore testing with sulphosalicylic acid is recommended.

Drug Interaction

Potentiation of warfarin-type anticoagulants has not been observed with concomitant ZANTAC administration. Likewise no clinically significant drug interactions have been observed between ZANTAC and theophylline or ZANTAC and diazepam. Drug interactions of this type are not expected since ranitidine does not significantly interact with the cytochrome P450 linked drug metabolizing enzyme system.

Carcinogenesis, mutagenesis and impairment of fertility

There was no indication of tumorigenic or carcinogenic effects in lifespan studies in mice and rats at doses up to 2000 mg/kg/day.

Ranitidine was not mutagenic in standard bacterial tests *(Salmonella, E. Coli)* for mutagenicity at concentrations up to the maximum recommended for these assays.

In a dominant lethal assay a single oral dose of 1000 mg/kg to male rats was without effect on the outcome of 2 matings per week for the next 9 weeks.

Usage in Pregnancy

Pregnancy Category B. Reproduction studies have been performed in rats and rabits at doses up to 160 times the human dose and have revealed no evidence of impaired fertility or harm to the fetus due to ZANTAC® (ranitidine hydrochloride). There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

Nursing Mothers

ZANTAC (ranitidine hydrochloride) is secreted in human milk. Caution should be exercised when ZANTAC is administered to a nursing mother.

Pediatric Use

Safety and effectiveness in children have not been established.

Use in Elderly Patients

Ulcer healing rates in elderly patients (65-82 years) were no different from those in younger age groups. The incidence rates for adverse events and laboratory abnormalities were also not different from those seen in other age groups.

ADVERSE REACTIONS

Headache has been found to be more frequent in ZANTAC®-treated patients (3%) than placebo-treated patients (2%). The following symptoms have been reported in ZANTAC-treated patients with a frequency of 1% or less: malaise, dizziness, constipation, nausea, abdominal pain and rash.

Decreases in white blood cell and platelet count have occurred in a few patients. These did not lead to cessation of treatment and were clinically insignificant. There have been no reported cases of agranulocytosis or aplastic anemia. Some small increases in serum creatinine have been noted in patients receiving ZANTAC (ranitidine hydrochloride).

Some increases (up to 5 times the upper limit of normal in one case) in serum transaminases and gamma-glutamyl transpeptidase have been reported. Rare cases of hepatitis have been reported.

In normal volunteers, SGPT values were increased to at least twice the pre-treatment levels in 6 of 12 subjects receiving 100 mg q.i.d. IV for 7 days, and in 4 of 24 subjects receiving 50 mg q.i.d. IV for 5 days. This dose-related effect of the IV formulation suggests that ZANTAC is potentially hepatotoxic. In placebo controlled studies of the oral formulation involving 2437 patients (1358 receiving ranitidine and 1079 patients receiving placebo), with most patients treated 4-8 weeks, there was no difference in incidence of SGOT-SGPT elevations between the 2 groups.

No clinically significant interference with endocrine or gonadal function have been reported.

OVERDOSAGE: There is no experience to date with deliberate overdosage. The usual measures to remove unabsorbed material from the gastrointestinal tract, clinical monitoring and supportive therapy should be employed.

Studies in animals receiving doses of ZANTAC® in excess of 225 mg/kg/d have shown muscular tremors, vomiting, and rapid respiration. Single oral doses of 1000 mg/kg in mice and rats were not lethal. Intravenous LD_{50} values in rat and mouse were 83 mg/kg and 77 mg/kg, respectively.

DOSAGE AND ADMINISTRATION:

Duodenal Ulcer

The current recommended adult oral dosage of ZANTAC® for duodenal ulcer is 150 mg twice daily, the only dose shown to speed healing of duodenal ulcer in U.S. clinical trials. Smaller doses have been shown to be equally effective in inhibiting gastric acid secretion in U.S. studies, and several foreign trials have shown that 100 mg b.i.d. is as effective as the 150 mg dose.

Antacids given concomitantly and as needed for relief of pain do not interfere with the absorption of ZANTAC.

Since 37% of patients can be expected to show complete healing at the end of two weeks, endoscopy at that time may spare many patients an additional period of treatment.

Pathological Hypersecretory Conditions

(such as Zollinger-Ellison Syndrome)

Recommended adult oral dosage: 150 mg twice a day. In some patients it may be necessary to administer ZANTAC 150 mg doses more frequently. Doses should be adjusted to individual patient needs, and should continue as long as clinically indicated. Doses up to 6 g/day have been employed in patients with severe disease.

Dosage adjustment for patients with impaired renal function.

On the basis of experience with a group of subjects with severely impaired renal function treated with ZANTAC, the recommended dose in patients with a creatinine clearance less than 50 ml/min is 150 mg every 24 hours. Should the patient's condition require, the frequency of dosing may be increased to every 12 hours or even further with caution. Hemodialysis reduces the level of circulating ranitidine. Ideally, the dosage schedule should be adjusted so that the timing of a scheduled dose coincides with the end of hemodialysis.

HOW SUPPLIED

ZANTAC® Tablets (ranitidine hydrochloride equivalent to 150 mg ranitidine) are white tablets embossed with "ZANTAC 150" on one side and "Glaxo" on the other. They are available in bottles of 30 tablets (NDC 0173-0344-40), 60 tablets (NDC 0173-0344-42), and unit dose packs of 100 tablets (NDC 0173-0344-47).

Store at controlled room temperature in a dry place. Protect from light. Replace cap securely after each opening. Manufactured for Glaxo Inc., Research Triangle Park, NC 27709 by Glaxo Operations UK Ltd, Greenford, England.

Issued Sept. 1983

Glaxo

Glaxo Inc., Research Triangle Park, NC 27709

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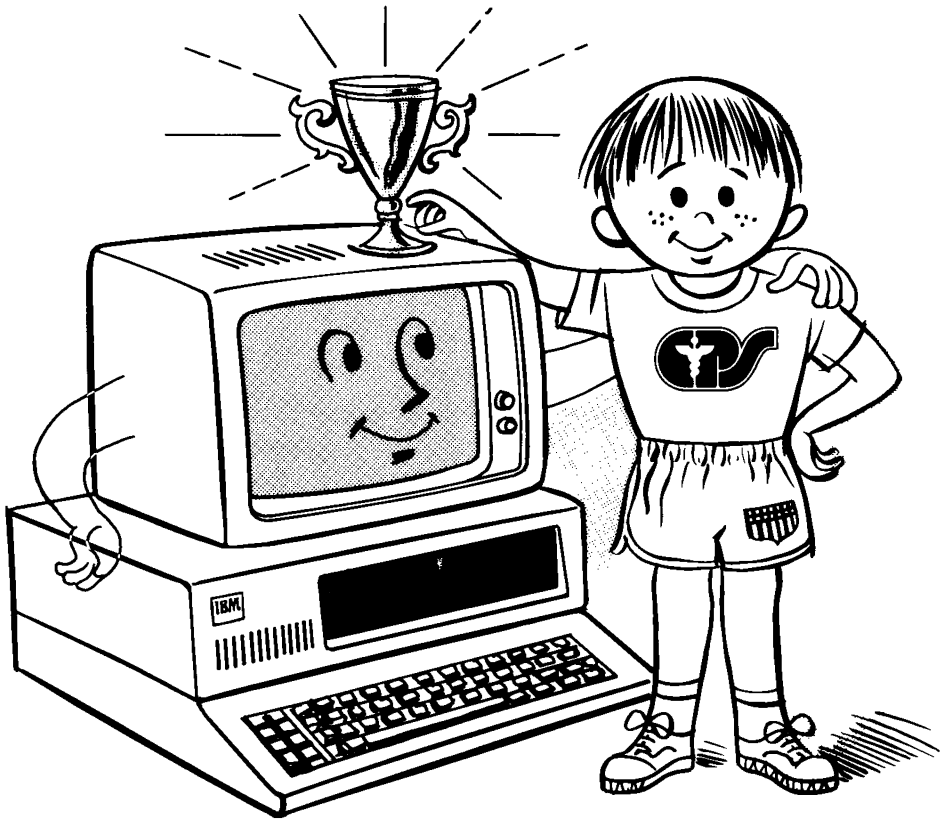

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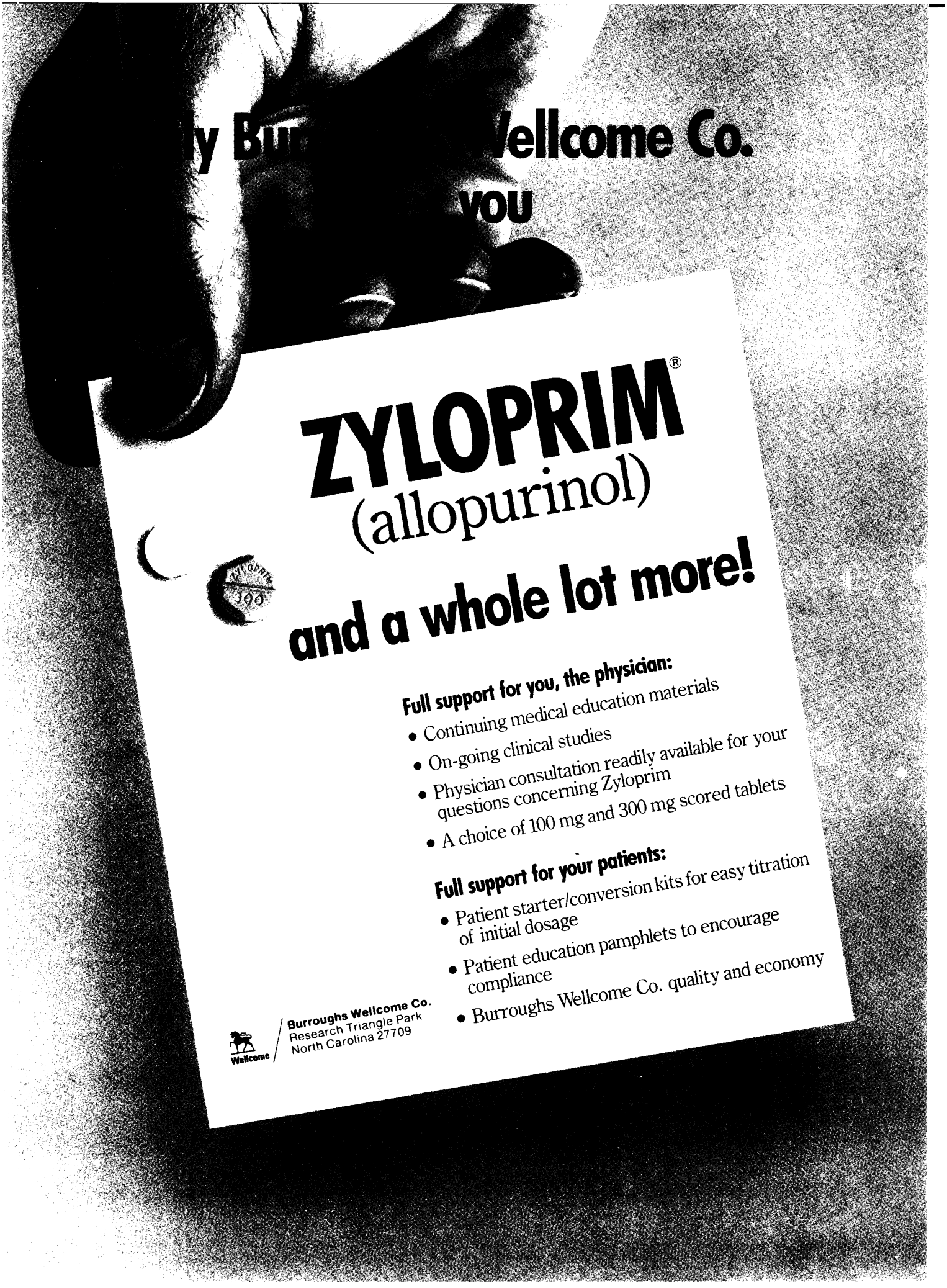
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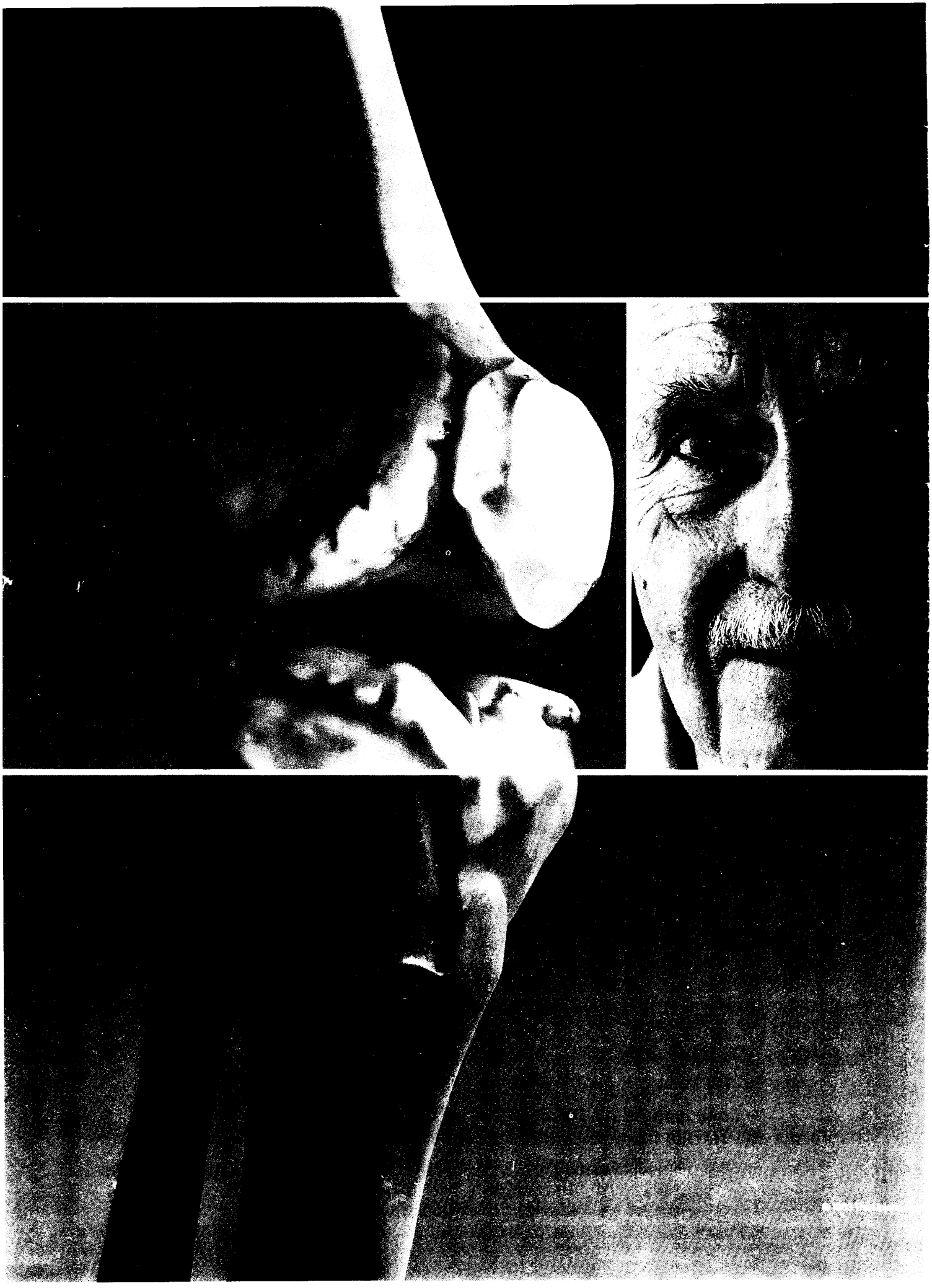


Arthritis pain after 50

Age is no barrier to the benefits of Motrin 600 mg tablets

The pain-relieving power of *Motrin* 600 mg tablets is welcome at any age. The advantages of *Motrin* become more important as patients grow older.

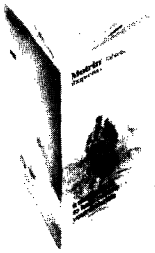
Advanced age has little or no influence on the pharmacokinetics of *Motrin.*

Motrin is as effective as indomethacin in relieving arthritis pain and inflammation. *Motrin* causes significantly fewer CNS effects and about half as many GI complaints as indomethacin.

Motrin relieves pain as effectively as a combination of aspirin 650 mg plus codeine 60 mg, as documented in analgesia studies.

Motrin has no significant effect on clotting factors in patients on coumarin-type anticoagulants in controlled studies. *Motrin* should be used with caution in persons with intrinsic coagulation defects and in those on anticoagulant therapy.

Motrin is rapidly metabolized and does not accumulate. *Motrin* provides better control of therapy, rapid response to dosage adjustment, and permits tailoring dosage to each patient's needs.



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Motrin® 600 mg TABLETS
(ibuprofen)

One tablet t.i.d.

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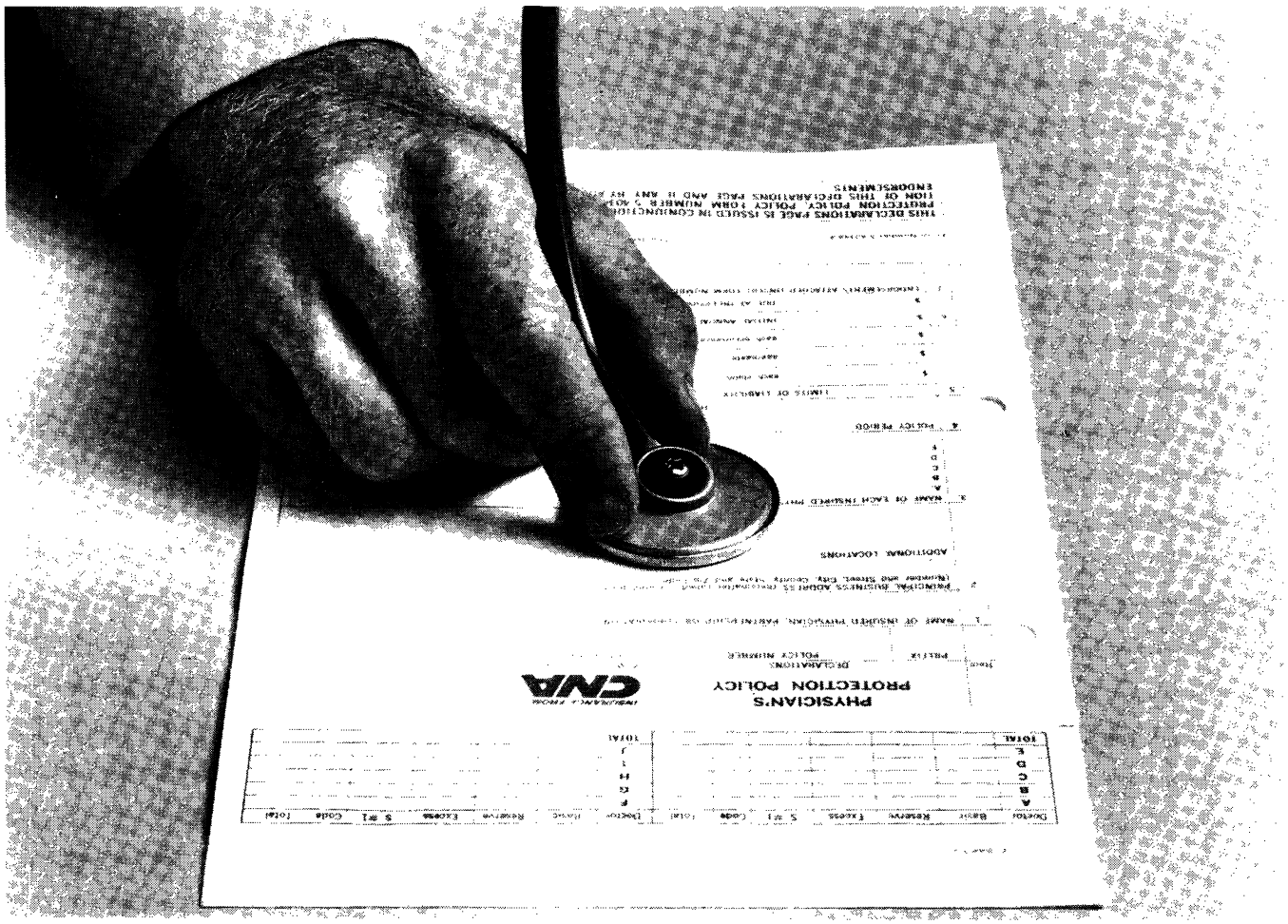
Upjohn The Upjohn Company
Kalamazoo, Michigan 49001



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NEW MEXICO 98TH

WEDNESDAY, MAY 2

2:00 pm House of Delegates, First Session
Guest Speaker: Harrison L. Rogers, Jr, MD
Speaker, AMA House of Delegates

3:00 pm Reference Committees

6:30 pm President's Reception and Banquet

THURSDAY, MAY 3

UPDATE ON ALCOHOLISM 1984
8:30 am-12 noon

Introduction and Overview
John D. Abrums, MD, President, American Society of Internal Medicine

Roots of Alcoholism and Alcohol Addiction
Maxwell N. Weisman, MD, Past President, American Medical Society on Alcoholism

Is Alcoholism a Problem in New Mexico?
Lane Leckman, MD, Director, Alcohol Treatment Program,
Department of Psychiatry, University of New Mexico School of Medicine

CURRENT CONTROVERSIES—PANEL DISCUSSION

Controlled Drinking versus Total Abstinence
William Miller, PhD, Department of Psychology, University of New Mexico

Heredity and Biochemistry
Gaynor C. Wild, PhD, Department of Biochemistry, University of New Mexico

Fetal Alcohol Syndrome
Carol Clericuzio, MD, Department of Pediatrics,
University of New Mexico School of Medicine

RECOGNITION AND TREATMENT
2:00 pm-5:00 pm

"Operation Cork"—A film presentation

Recognition in Patients—M. N. Weisman, MD

MEDICAL SOCIETY

ANNUAL MEETING

MAY 2-4, 1984
SANTA FE HILTON INN

Recognition in Colleagues
Morris McEwen, MD, Chairman, Physicians Aid Committee,
New Mexico Medical Society

Consequences of Nonrecognition
Jeremiah Turcotte, MD, Chairman, Dep artment of Surgery,
University of Michigan Medical School

6:30 pm Specialty Society Dinners

FRIDAY, MAY 4

HEALTH IN THE WORKPLACE
9:00 am-12 noon

Occupational Health Hazards in New Mexico
William Wiese, MD, Chief, Department of Community Medicine,
University of New Mexico School of Medicine

Video Display Terminals
Jacqueline Messite, MD, Regional Program Consultant, Region II,
National Institute of Occupational Safety and Health

Stress in the Workplace
Dick Papanfus, PhD, Department of Health Physical Education and Recreation,
University of New Mexico

Occupational Hazards of Health Professionals
Jacqueline Messite, MD

Recognition of Problems
Jonathan M. Samet, MD, Department of Medicine,
University of New Mexico School of Medicine

The Real World—Panel Discussion
Responsibility—Workers' Compensation—Occupational Safety and Health

12:30 pm NEMPAC Luncheon—Sheraton Inn

2:00 pm House of Delegates, Second Session

For Further Information or Registration Material

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1984 SCIENTIFIC SESSION

FRIDAY, MAY 4, 1984

CME Credits: AMA Category I, AAFP Credits, CE Units for Nurses
Registration: 8:00 am - 9:00 am (continental breakfast)
Program Chairman: Stephen A. Kollins, M.D.

9:00 am — Introductions

9:15 am — "Percutaneous Nephrolithotomy: New Approaches to Renal Stone Disease"
Robert Kahn, M.D., *Assistant Professor of Urology at the University of California Medical Center, San Francisco, California*

10:00 am — "Light Transmission Mammography and Evaluation of the Breast"
Ernest Carlsen, Ph.D., M.D., *Department of Radiology at Jerry Pettis Memorial Hospital in Loma Linda, California*

10:45 am — Refreshment Break

11:00 am — "Low Level Radioactive Waste Disposal: Prospectives for Nevada Physicians"
Schuyler Hilts, M.D., *President-Elect of the American College of Nuclear Physicians*

11:45 am — Panel—Questions & Answers

12:15 pm — Luncheon and Presentation: "Post Tefra Planning Techniques for Turning Income Tax Dollars into Family Wealth"
Mr. Gary Sheets, Financial Advisor for Coordinated Financial Services, Inc.

1:45 pm — "Magnetic Resonance Imaging: New Horizons in Diagnosis"
William Bradley, M.D., Ph.D., *Director of the NMR Imaging Laboratory at the Huntington Medical Research Institute in Pasadena, California*

2:45 pm — "Osteoporosis: The Hidden Threat for Women"
Ian V. Jones, M.D., *Head of the Division of Obstetrics and Gynecology at the Scripps Clinic and Research Foundation, La Jolla, California*

3:30 pm — Panel—Questions & Answers

4:00 pm — Adjournment

LAS VEGAS

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Nonmember physicians	$110
Nurses	$ 50
Retired, Interns, Students	$ 25

Return this form along with appropriate fees to the NEVADA STATE MEDICAL ASSOCIATION, 3660 Baker Lane, Reno, NV 89509. Or register by phone, (702) 825-6788, Kathy Boyce, Convention Manager. Housing information will be forwarded upon receipt of registration form.

Before prescribing, see complete prescribing information in SK&F CO. literature or *PDR*. The following is a brief summary.

* **WARNING**

This drug is not indicated for initial therapy of edema or hypertension. Edema or hypertension requires therapy titrated to the individual. If this combination represents the dosage so determined, its use may be more convenient in patient management. Treatment of hypertension and edema is not static, but must be reevaluated as conditions in each patient warrant.

Contraindications: Concomitant use with other potassium-sparing agents such as spironolactone or amiloride. Further use in anuria, progressive renal or hepatic dysfunction, hyperkalemia. Pre existing elevated serum potassium. Hypersensitivity to either component or other sulfonamide derived drugs.

Warnings: Do not use potassium supplements, dietary or otherwise, unless hypokalemia develops or dietary intake of potassium is markedly impaired. If supplementary potassium is needed, potassium tablets should not be used. Hyperkalemia can occur and has been associated with cardiac irregularities. It is more likely in the severely ill, with urine volume less than one liter/day, the elderly and diabetics with suspected or confirmed renal insufficiency. Periodically, serum K^+ levels should be determined. If hyperkalemia develops, substitute a thiazide alone, restrict K^+ intake. **Associated widened QRS complex or arrhythmia requires prompt additional therapy.** Thiazides cross the placental barrier and appear in cord blood. Use in pregnancy requires weighing anticipated benefits against possible hazards, including fetal or neonatal jaundice, thrombocytopenia, other adverse reactions seen in adults. Thiazides appear and triamterene may appear in breast milk. If their use is essential, the patient should stop nursing. Adequate information on use in children is not available. Sensitivity reactions may occur in patients with or without a history of allergy or bronchial asthma. Possible exacerbation or activation of systemic lupus erythematosus has been reported with thiazide diuretics.

Precautions: Do periodic serum electrolyte determinations (particularly important in patients vomiting excessively or receiving parenteral fluids, and during concurrent use with amphotericin B or corticosteroids or corticotropin [ACTH]). Periodic BUN and serum creatinine determinations should be made, especially in the elderly, diabetics or those with suspected or confirmed renal insufficiency. Cumulative effects of the drug may develop in patients with impaired renal function. Thiazides should be used with caution in patients with impaired hepatic function. They can precipitate coma in patients with severe liver disease. Observe regularly for possible blood dyscrasias, liver damage, other idiosyncratic reactions. Blood dyscrasias have been reported in patients receiving triamterene, and leukopenia, thrombocytopenia, agranulocytosis, and aplastic and hemolytic anemia have been reported with thiazides. Thiazides may cause manifestation of latent diabetes mellitus. The effects of oral anticoagulants may be decreased when used concurrently with hydrochlorothiazide; dosage adjustments may be necessary. Clinically insignificant reductions in arterial responsiveness to norepinephrine have been reported. Thiazides have also been shown to increase the paralyzing effect of nondepolarizing muscle relaxants such as tubocurarine. Triamterene is a weak folic acid antagonist. Do periodic blood studies in cirrhotics with splenomegaly. Antihypertensive effects may be enhanced in post sympathectomy patients. Use cautiously in surgical patients. Triamterene has been found in renal stones in association with the other usual calculus components. Therefore, Dyazide should be used with caution in patients with histories of stone formation. A few occurrences of acute renal failure have been reported in patients on Dyazide when treated with indomethacin. Therefore, caution is advised in administering nonsteroidal anti-inflammatory agents with Dyazide. The following may occur: transient elevated BUN or creatinine or both, hyperglycemia and glycosuria (diabetic insulin requirements may be altered), hyperuricemia and gout, digitalis intoxication (in hypokalemia), decreasing alkali reserve with possible metabolic acidosis. Dyazide interferes with fluorescent measurement of quinidine. Hypokalemia is uncommon with Dyazide, but should it develop, corrective measures should be taken such as potassium supplementation or increased dietary intake of potassium-rich foods. Corrective measures should be instituted cautiously and serum potassium levels determined. Discontinue corrective measures and Dyazide should laboratory values reveal elevated serum potassium. Chloride deficit may occur as well as dilutional hyponatremia. Concurrent use with chlorpropamide may increase the risk of severe hyponatremia. Serum PBI levels may decrease without signs of thyroid disturbance. Calcium excretion is decreased by thiazides. Dyazide should be withdrawn before conducting tests for parathyroid function.

Thiazides may add to or potentiate the action of other antihypertensive drugs.

Diuretics reduce renal clearance of lithium and increase the risk of lithium toxicity.

Adverse Reactions: Muscle cramps, weakness, dizziness, headache, dry mouth, anuria/oliguria, rash, urticaria, photosensitivity, purpura, other dermatological conditions; nausea and vomiting, diarrhea, constipation, other gastrointestinal disturbances, postural hypotension (may be aggravated by alcohol, barbiturates, or narcotics). Necrotizing vasculitis, paresthesias, icterus, pancreatitis, xanthopsia and respiratory distress including pneumonitis and pulmonary edema. Transient blurred vision, sialadenitis, and vertigo have occurred with thiazides alone. Triamterene has been found in renal stones in association with other usual calculus components. Rare incidents of acute interstitial nephritis have been reported. Impotence has been reported in a few patients on Dyazide, although a causal relationship has not been established.

Supplied: Dyazide is supplied as a maroon and white capsule, in bottles of 1000 capsules; Single Unit Packages (unit-dose) of 100 (intended for institutional use only); in Patient-Pak™ unit-of-use bottles of 100.

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Serum K^+ and BUN should be checked periodically (see Warnings and Precautions).

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DIRECTOR OF SURGICAL SERVICES—233-bed teaching hospital with residencies in OB/GYN, Surgery, Medicine, and Family Practice is seeking a Director of Surgical Services. Position available July 1, 1984. Responsible for administration and supervision of patient care and surgical training program. Candidates should be Board certified in General Surgery and have significant experience in administrative and teaching responsibility. Experience in a training program is preferred. Salary negotiable depending on background and experience. Hospital is located in beautiful San Joaquin County, close to major cities and skiing. For additional information, please submit CV and references or contact J. D. Kortzeborn, MD, Medical Director, San Joaquin General Hospital, P.O. Box 1020, Stockton, CA 95201; (209) 982-1800, Ext. 3052. Affirmative Action/Equal Opportunity Employer.

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FAMILY PRACTICE—NORTH IDAHO: ABFP or eligible to join low-key, but busy practice, excellent and beautiful family area. Lab, x-ray on premises, 24 hour ER coverage. Terms negotiable. Call (208) 773-1577 or respond with CV to 2209 Canyon Dr., Coeur d'Alene, ID 83814.

MINOR EMERGENCY CLINIC: Full-time physician opening for the Sacramento area. One year contract minimum. Malpractice coverage provided. Dr Kendall Bauer, 815 Mast Ct, Folsom, CA 95630; (916) 933-1449 evenings.

PHYSICIANS WANTED

EMERGENCY PHYSICIAN—For community hospital in Southern California. Competitive salary, malpractice paid. Eight 24 hour shifts/month. Minimum 3 years emergency medicine experience, Board certification, or Board eligible by residency. Send CV to: Dr Charles Magee, Ontario Emergency Group, 550 North Monterey Ave, Ontario, CA 91764 or call: (714) 980-2226.

PEDIATRICIAN BC/BE to join three young progressive pediatricians in growing area of Salt Lake City. Superb access to outdoor activities. New hospital facilities adjacent. Contact Chuck Norlin, MD, 3449 South 4155 West, West Valley City, UT 84120.

SOUTHERN CALIFORNIA HMO seeking experienced specialists and General Practitioners for health care centers in Los Angeles and Orange Counties. CIGNA Healthplans of California, formerly INA and Ross Loos Healthplans, offers competitive salaries and excellent benefits. Opportunity to join an established, growing and progressive company. CV to: Director/Physician Recruitment, CIGNA Healthplans of California, 700 N Brand Blvd, Suite 500, Glendale, CA 91203.

PHYSICIANS WANTED

SOUTHERN CALIFORNIA: HMO seeking experienced specialists and general practitioners for health care centers in Los Angeles and Orange Counties. INA and Ross Loos Healthplans is part of CIGNA Healthplans, Inc., the largest investor-owned operator of prepaid healthplans in the nation. Competitive salaries, excellent benefits. Opportunity to join an established, growing and progressive company. CV to: Professional Placement, INA and Ross Loos Healthplans, 700 N. Brand Blvd, Suite 500, Glendale, CA 91203.

FAMILY MEDICINE FACULTY POSITIONS. Due to expansion, the Department of Family Practice at the San Bernardino County Medical Center is recruiting for immediate vacancies, as well as vacancies for July 1984. This academic department of 17 faculty members is seeking Board certified Family Physicians with prior teaching experience in Family Medicine. Demonstrated research activities are desired. Send inquiries and curriculum vitae to: Merrill N. Werblun, MD, Chairman, Department of Family Practice, P.O. Box 3571, San Bernardino, CA 92413.

SAN FRANCISCO BAY AREA—50 MD multispecialty private group practice established 25 years ago, seeking a well-qualified OBSTETRICIAN GYNECOLOGIST to join our busy 4-physician department in their general OB/GYN work. Excellent location in the Santa Clara Valley, 45 minutes from San Francisco, 10 minutes from Stanford University. Send CV to: Recruitment Committee, P.O. Box 3496, Sunnyvale, CA 94088-3496.

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(Continued on Page 488)

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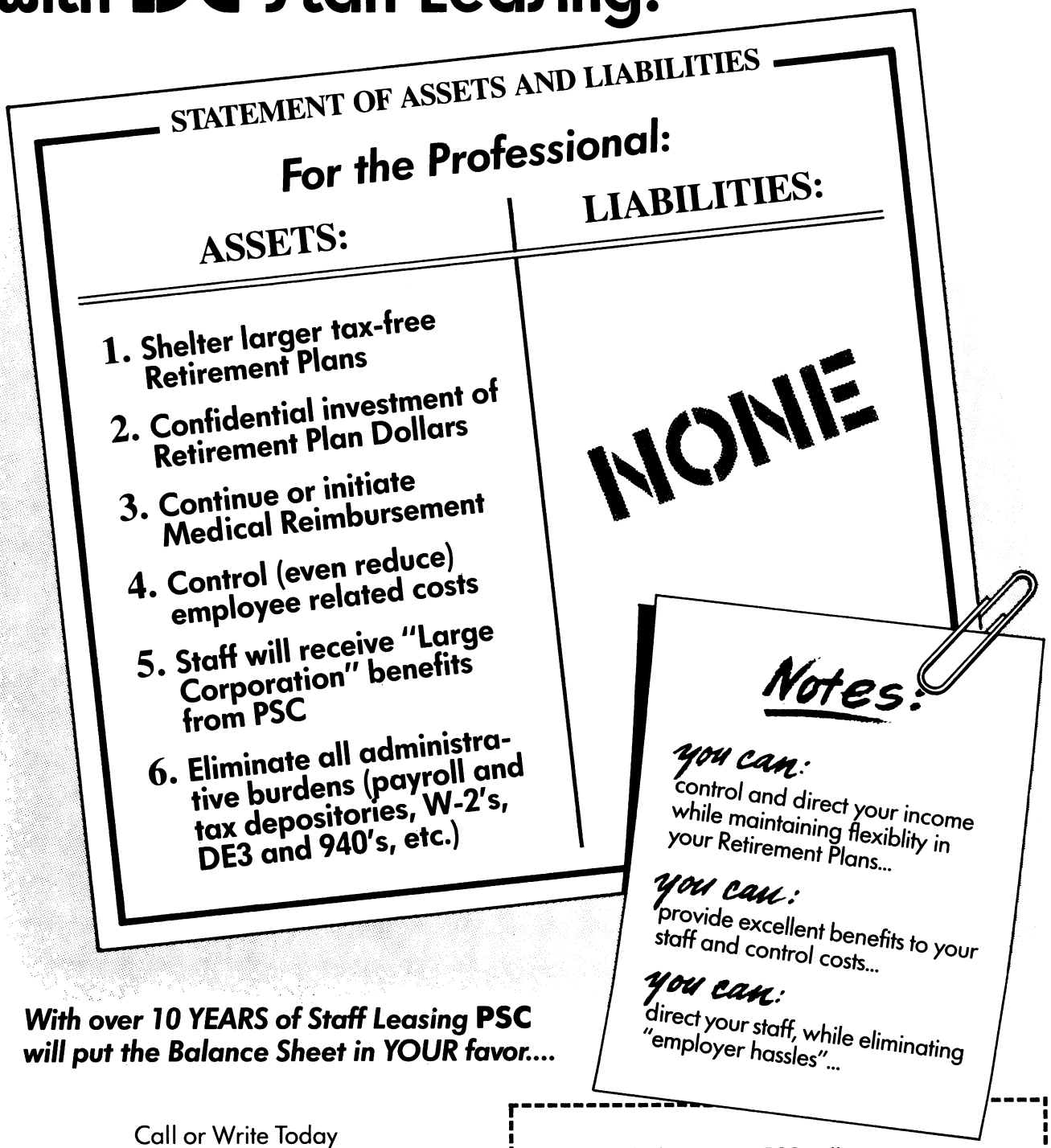

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OBSTETRICIAN & GYNECOLOGIST—needed for expanding HMO in Southern California. Multi-specialty group with facilities in Los Angeles and Orange Counties. CV to: Director/Physician Recruitment, CIGNA Healthplans of California, 700 N Brand Blvd, Suite 500, Glendale, CA 91203.

FAMILY PRACTITIONERS CALIFORNIA—Family Practitioners—Board certified or eligible Family Practitioners for traditional primary care center. Experience in family practice and occupational medicine in group practice or clinic setting preferred. Understanding of prepaid medicine helpful. One position available in attractive northern LA County desert community of Lancaster, and one in metropolitan LA financial district. Outstanding salary, full benefits, and profit sharing. Regular hours. Qualified applicants please submit CVs to: A. Scarsella, MD, Medical Director, Convenience Care Centers, P.O. Box 5780, Los Angeles, CA 90055.

WASHINGTON, TACOMA: EMERGENCY MEDICINE position is available May 1984 in a 150 bed, moderate volume hospital emergency department. Guaranteed income with incentive compensation plan and paid malpractice insurance. Contact: EMS, 4010 Dupont Circle, Suite 700, Louisville, KY 40207, 1 (800) 626-2040.

MEDICAL DIRECTOR—ADULT CARE UNIT, San Francisco. Immediate opening. Marshal Hale Memorial Hospital is seeking an enthusiastic licensed physician with experience or specialty training in alcohol and drug rehabilitation to become Medical Director of the Adult Alcohol-Chemical Dependency Rehabilitation Care Unit located at the hospital. Address inquiries to Dr Alan Rosenstein (415) 386-7000.

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FAMILY PRACTICE, IDAHO—Multispecialty group needs Family Physician for satellite clinic in 4 season resort area. Combination salary and incentive plan. Send CV to Alan Stevenson, Moritz Community Hospital, Box 86, Sun Valley, ID 83353.

CALIFORNIA—URGENT CARE. Positions available for Spring 1984 in free-standing, urgent care settings in several locations. Board certication or eligibility in Emergency Medicine, Family Practice or related specialty required. Opportunities exist for directorships for physicians with appropriate experience. Guaranteed minimum, malpractice paid, benefit package available. Contact: California Emergency Physicians, 440 Grand Avenue, Suite 500, Oakland, CA 94610, (415) 832-6400.

PRIMARY CARE PHYSICIAN—(General Practitioner or General Internist) for employment by the State of California at San Quentin Prison Hospital. Civil service status. Forty hours per week. Beginning salary $42,792-$61,464 depending on qualifications and experience. For further information contact: Jack J. Williams, MD, at (415) 454-1460.

ED PHYSICIAN, TACOMA, WASHINGTON: Experienced (3 yr. plus) or Boarded ED Physicians needed for locum tenens positions (2) to begin May 1 to June 1, 1984, and to continue for 4-6 months. Established group with two hospitals. Possibility of continuation if mutually agreeable. Reply with CV to: Mike Doman, MD, 1700 36th Ave., Seattle, WA 98122; (206) 323-4914 (home) or (206) 597-7600 (work).

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EMERGENCY PHYSICIAN—Perm. hospital position available July 1984. Board prepared in FP or EM or 2 or more years EM experience. Other training may be substituted if appropriate. Competitive remuneration, malpractice paid. Located in Central California's San Joaquin Valley. Superior lifestyle, excellent family environment. 112 bed acute care hospital, base station approved. Excellent ancillary services. Send CV to AC Jaramillo, MD, EM, Medical Director—Tulare District Hospital, 869 Cherry St, Tulare, CA 93274.

FAMILY PRACTICE. Physician needed in western Oregon—solo or association. Population 40,000; 106 bed acute care hospital with new ancillary building and new whole body CAT Scanner. Office space available now. Contact J. C. Keever, MD, Medical Director, McKenzie-Willamette Hospital, 1460 G Street, Springfield, OR 97477; (503) 726-4580.

OREGON—FAMILY PRACTICE PHYSICIAN with interest in OB sought for multispecialty group. Beautiful rural community, 38 miles from Portland. Send CV to Adm, 420 E. 5th St, McMinnville, OR 97128 and phone to FP staff member (503) 472-6161.

THE DEPARTMENT OF MEDICINE, UNIVERSITY OF CALIFORNIA, SAN FRANCISCO is seeking medical oncologist at the Clinical Assistant Professor level to assist in patient care, teaching and research activities at San Francisco General Hospital. Must be Board Certified in Internal Medicine, Board Certified/Eligible in Oncology. Should have demonstrated experience in basic research especially in areas relevant to clinical trials and epidemiology of AIDS/Kaposi's Sarcoma. Send letter of application with curriculum vitae and bibiliography to: Paul Volberding, MD, San Francisco General Hospital, 1001 Portero Ave., Room 5H22, San Francisco, CA 94110. The University of California is an Affirmative Action, Equal Opportunity Employer.

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FAMILY PHYSICIAN OR INTERNIST—To work in primary care practice in Chino, Calif. Competitive compensation with opportunity for ownership. Send CV to: Dr Charles Magee, 9681 Hidden Farm Road, Alta Loma, CA 91701, or call: (714) 980-2226.

GASTROENTEROLOGIST, Board Int. Med. and Board eligible GI, to join 36 member multi-specialty group located on the central coast of California. Premium location, excellent practice opportunity with fully paid benefit and retirement program; guaranteed salary first six months followed by incentive pay program; all practice costs paid. Replies to: Box 6411, Western Journal of Medicine, 44 Gough St., San Francisco, CA 94103.

PHYSICIANS WANTED

GENERAL INTERNAL MEDICINE SPECIALIST position open with 37-member multi-specialty group. Excellent practice opportunity; full range of benefits; early shareholder status; all practice costs paid. Prefer recent residency trained physicians. For more information contact: Daniel Small, MD, Medical Director, or David Graham, Asst Administrator, San Luis Medical Clinic, Ltd., 1235 Osos St, San Luis Obispo, CA 93401.

LOCUM TENENS

LOCUM TENENS needed to cover Family Practice from May 21, 1984 through June 15, 1984. Must have California license. Contact Mr R. Reesh, Administrator, Granger Medical Group, Inc., 140 E. Granger Ave, Modesto, CA 95350; (209) 529-0531.

LOCUM TENENS SERVICE
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. . . offers coverage for vacation or continuing education. To arrange coverage for your practice or to participate as temporary physician, contact: **Carol Sweig, Director, 1124 Ballena, Alameda, CA 94501; (415) 521-4110.**

SITUATIONS WANTED

PERMANENT PHYSICIAN PLACEMENT SERVICE. Western Physicians Registry. Physicians available for primary care and specialty placement. Varied opportunities for physicians. Contact Cynthia Selfridge, Director, (415) 521-4110, 1124 Ballena, Alameda, CA 94501.

ALLERGIST. Board certified and recertified Allergist and Board certified Pediatrician desires part-time practice allergy-immunology-adult and pediatrics or locum tenens. Prefers Los Angeles and desert area. Reply Box 6420, Western Journal of Medicine, 44 Gough St, San Francisco, CA 94103.

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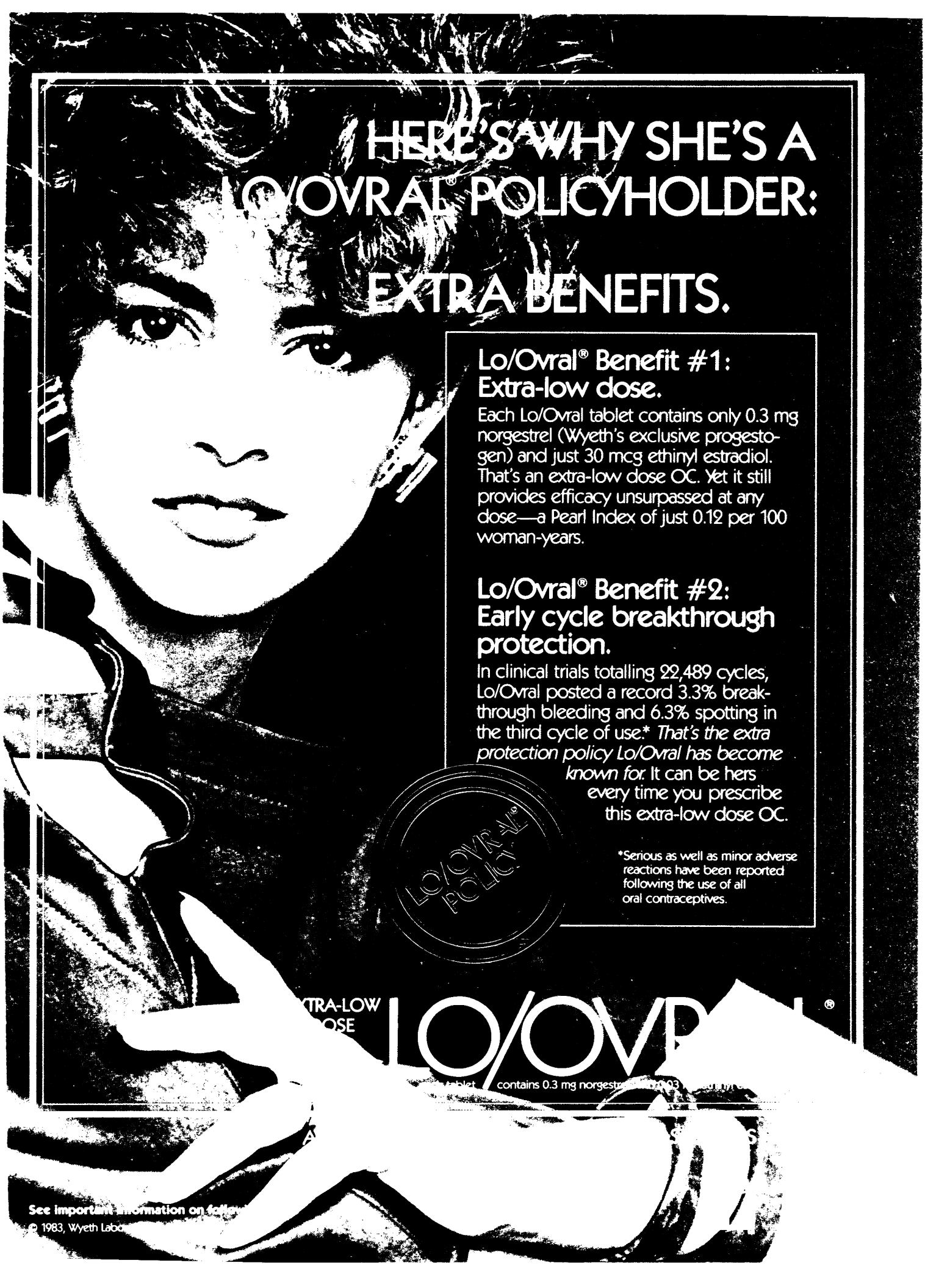
(Continued on Page 500)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Indications and Usage—LO/OVRAL® is indicated for the prevention of pregnancy in women who elect to use oral contraceptives (OC's) as a method of contraception.

Contraindications—OC's should not be used in women with any of the following conditions: 1. Thrombophlebitis or thromboembolic disorders. 2. A past history of deep-vein thrombophlebitis or thromboembolic disorders. 3. Cerebral-vascular or coronary-artery disease. 4. Known or suspected carcinoma of the breast. 5. Known or suspected estrogen-dependent neoplasia. 6. Undiagnosed abnormal genital bleeding. 7. Known or suspected pregnancy (see Warning No. 5). 8. Benign or malignant liver tumor which developed during use of OC's or other estrogen-containing products.

Warnings

Cigarette smoking increases the risk of serious cardiovascular side effects from oral contraceptive use. This risk increases with age and with heavy smoking (15 or more cigarettes per day) and is quite marked in women over 35 years of age. Women who use oral contraceptives should be strongly advised not to smoke.

The use of oral contraceptives is associated with increased risk of several serious conditions, including thromboembolism, stroke, myocardial infarction, hepatic adenoma, gallbladder disease, hypertension. Practitioners prescribing oral contraceptives should be familiar with the following information relating to these risks.

1. *Thromboembolic Disorders and Other Vascular Problems*—An increased risk of thromboembolic and thrombotic disease associated with use of OC's is well established. Three principal studies in Great Britain and 3 in the U.S. have demonstrated increased risk of fatal and nonfatal venous thromboembolism and stroke, both hemorrhagic and thrombotic. These studies estimate that users of OC's are 4 to 11 times more likely than nonusers to develop these diseases without evident cause.

CEREBROVASCULAR DISORDERS—In a collaborative American study of cerebrovascular disorders in women with and without predisposing causes, it was estimated that the risk of hemorrhagic stroke was 2.0 times greater in users than nonusers and the risk of thrombotic stroke was 4 to 9.5 times greater in users than in nonusers.

MYOCARDIAL INFARCTION (MI)—An increased risk of MI associated with use of OC's has been reported, confirming a previously suspected association. These studies, conducted in the UK, found, as expected, that the greater the number of underlying risk factors for coronary artery disease (cigarette smoking, hypertension, hypercholesterolemia, obesity, diabetes, history of pre-eclamptic toxemia) the higher the risk of developing MI, regardless of whether the patient was an OC user or not. OC's, however, were found to be a clear additional risk factor. In terms of relative risk, it has been estimated that OC users who do not smoke (smoking is considered a major predisposing condition to MI) are about twice as likely to have a fatal MI as nonusers who do not smoke. OC users who are also smokers have about a 5-fold increased risk of fatal MI compared to users who do not smoke, but about a 10- to 12-fold increased risk compared to nonusers who do not smoke. Furthermore, amount of smoking is also an important factor. In determining importance of these relative risks, however, baseline rates for various age groups must be given serious consideration. Importance of other predisposing conditions mentioned above in determining relative and absolute risks has not as yet been quantified; quite likely the same synergistic action exists, but perhaps to a lesser extent.

RISK OF DOSE—In an analysis of data derived from several national adverse-reaction reporting systems, British investigators concluded that risk of thromboembolism, including coronary thrombosis, is directly related to dose of estrogen in OC's. Preparations containing 100 mcg or more of estrogen were associated with higher risk of thromboembolism than those containing 50-80 mcg. Their analysis did suggest, however, that quantity of estrogen may not be the sole factor involved. This finding has been confirmed in the U.S.

ESTIMATE OF EXCESS MORTALITY FROM CIRCULATORY DISEASES—A large prospective study carried out in the UK estimated the mortality rate per 100,000 women per year from diseases of the circulatory system for users and nonusers of OC's according to age, smoking habits, and duration of use. Overall excess death rate annually from circulatory diseases for OC users was estimated to be 20 per 100,000 (ages 15-34—5/100,000; ages 35-44—33/100,000; ages 45-49—140/100,000), risk being concentrated in older women, in those with long duration of use, and in cigarette smokers. It was not possible, however, to examine interrelationships of age, smoking, and duration of use, nor to compare effects of continuous vs. intermittent use. Although the study showed a 10-fold increase in death due to circulatory diseases in users for 5 or more years, all these deaths occurred in women 35 or older. Until larger numbers of women under 35 with continuous use for 5 or more years are available, it is not possible to assess magnitude of relative risk for this younger group. Available data from a variety of sources have been analyzed to estimate risk of death associated with various methods of contraception. Estimates of risk of death for each method include combined risk of contraceptive method (e.g., thromboembolic and thrombotic disease in the case of OC's) plus risk attributable to pregnancy or abortion in event of method failure. This latter risk varies with effectiveness of method. The study concluded that mortality associated with all methods of birth control is low and below that associated with childbirth, with the exception of OC's in women over 40 who smoke. Lowest mortality is associated with condom or diaphragm backed up by early abortion. Risk of thromboembolic and thrombotic disease associated with OC's increases with age after about 30 and, for MI, is further increased by hypertension, hypercholesterolemia, obesity, diabetes, or history of pre-eclamptic toxemia, and especially cigarette smoking. Physician and patient should be alert to earliest manifestations of thromboembolic and thrombotic disorders (e.g., thrombophlebitis, pulmonary embolism, cerebrovascular insufficiency, coronary occlusion, retinal thrombosis, and mesenteric thrombosis). Should any of these occur or be suspected, the drug should be discontinued immediately.

A 4- to 6-fold increased risk of postsurgery thromboembolic complications has been reported in OC users.

If feasible, OC's should be discontinued at least 4 weeks before surgery of a type associated with increased risk of thromboembolism or prolonged immobilization.

2. *Ocular Lesions*—There have been reports of neuro-ocular lesions such as optic neuritis or retinal thrombosis associated with use of OC's. Discontinue OC's if there is unexplained, sudden or gradual, partial or complete loss of vision; onset of proptosis or diplopia; papilledema; or retinal-vascular lesions, and institute appropriate diagnostic and therapeutic measures.

3. *Carcinoma*—Long-term continuous administration of either natural or synthetic estrogen in certain animal species increases frequency of carcinoma of the breast, cervix, vagina, and liver. Certain synthetic progestogens, none currently contained in OC's, have been noted to increase incidence of mammary nodules, benign and malignant, in dogs. In humans, 3 case-control studies have reported an increased risk of endometrial carcinoma associated with prolonged use of exogenous estrogen in postmenopausal women. One publication reported on the first 21 cases submitted by physicians to a registry of cases of adenocarcinoma of the endometrium in women under 40 on OC's. Of cases found in women without predisposing risk factors (e.g., irregular bleeding at the time OC's were first given, polycystic ovaries), nearly all occurred in women who had used a sequential OC. These are no longer marketed. No evidence has been reported suggesting increased risk of endometrial cancer in users of conventional combination or progestogen-only OC's. Several studies have found no increase in breast cancer in women taking OC's or estrogens. One study, however, while also noting no overall increased risk of breast cancer in women on OC's, found an excess risk in subgroups of OC users with documented benign breast disease. Reduced occurrence of benign breast tumors in users of OC's has been well documented. In summary, there is at present no confirmed evidence from human studies of increased risk of cancer associated with OC's. Close clinical surveillance of all women on OC's is, nevertheless, essential. In all cases of undiagnosed persistent or recurrent abnormal vaginal bleeding, appropriate diagnostic measures should be taken to rule out malignancy. Women with a strong family history of breast cancer or with breast nodules, fibrocystic disease, or abnormal mammograms should be monitored with particular care if they elect to use OC's.

4. *Hepatic Tumors*—Benign hepatic adenomas have been found to be associated with use of OC's. One study showed that OC's with high hormonal potency were associated with higher risk than lower potency OC's. Although benign, hepatic adenomas may rupture and may cause death through intra-abdominal hemorrhage. This has been reported in short-term as well as long-term users. Two studies relate risk with duration of use of OC's, the risk being much greater after 4 or more years' use. While hepatic adenoma is rare, it should be considered in women presenting abdominal pain and tenderness, abdominal mass or shock. A few cases of hepatocellular carcinoma have been reported in women on OC's. Relationship of these drugs to this type of malignancy is not known.

5. *Use in or Immediately Preceding Pregnancy, Birth Defects in Offspring, and Malignancy in Female Offspring*—Use of female sex hormones—both estrogenic and progestational agents—during early pregnancy may seriously damage the offspring. It has been shown that females exposed in utero to diethylstilbestrol, a nonsteroidal estrogen, have increased risk of developing in later life a form of vaginal or cervical cancer ordinarily extremely rare. This risk has been estimated to be of the order of 1 in 1,000 exposures or less. Although there is no evidence now that OC's further enhance risk of developing this type of malignancy, such patients should be monitored with particular care if they elect to use OC's. Furthermore, 30 to 90% of such exposed women have been found to have epithelial changes of the vagina and cervix. Although these changes are histologically benign, it is not known whether this condition is a precursor of vaginal malignancy. Male children so exposed may develop abnormalities of the urogenital tract. Although similar data are not available with use of other estrogens, it cannot be presumed they would not induce similar changes. An increased risk of congenital anomalies, including heart defects and limb defects, has been reported with use of sex hormones, including OC's, in pregnancy. One case-control study estimated a 4.7-fold increase in risk of limb-reduction defects in infants exposed in utero to sex hormones (OC's, hormonal withdrawal tests for pregnancy, or attempted treatment for threatened abortion). Some exposures involved only a few days. Data suggest that risk of limb-reduction defects in exposed fetuses is somewhat less than 1 in 1,000 live births. In the past, female sex hormones have been used during pregnancy in an attempt to treat threatened or habitual abortion. There is considerable evidence that estrogens are ineffective for these indications, and there is no evidence from well-controlled studies that progestogens are effective. There is some evidence that triploidy and possibly other types of polyploidy are increased among abortuses from women who become pregnant soon after ceasing OC's. Embryos with these anomalies are virtually always aborted spontaneously. Whether there is an overall increase in spontaneous abortion of pregnancies conceived soon after stopping OC's is unknown. It is recommended that, for any patient who has missed 2 consecutive periods, pregnancy should be ruled out before continuing OC's. If the patient has not adhered to the prescribed schedule, the possibility of pregnancy should be considered at time of first missed period, and further use of OC's should be withheld until pregnancy has been ruled out. If pregnancy is confirmed, the patient should be apprised of the potential risks to the fetus, and advisability of continuation of the pregnancy should be discussed. It is also recommended that women who discontinue OC's with intent of becoming pregnant use an alternate form of contraception for a period of time before attempting to conceive. Many clinicians recommend 3 months, although no precise information is available on which to base this. The administration of progestogen-estrogen combinations to induce withdrawal bleeding should not be used as a test of pregnancy.

6. *Gallbladder Disease*—Studies report increased risk of surgically confirmed gallbladder disease in users of OC's and estrogens. In one study, increased risk appeared after 2 years' use and doubled after 4 or 5 years' use. In one of the other studies, increased risk was apparent between 6 and 12 months' use.

7. *Carbohydrate and Lipid Metabolic Effects*—Decrease in glucose tolerance has been observed in a significant percentage of patients on OC's. For this reason, prediabetic and diabetic patients should be carefully observed while on OC's. Increase in triglycerides and total phospholipids has been observed in patients on OC's; clinical significance of this finding remains to be defined.

8. *Elevated Blood Pressure*—Increase in blood pressure has been reported in patients on OC's. In some women, hypertension may occur within a few months of beginning OC's. In the 1st year of use, prevalence of women with hypertension is low in users and may be no higher than that of a comparable group of nonusers. Prevalence in users increases, however, with longer exposure, and in the 5th year of use is 2½ to 3 times the reported prevalence in the 1st year. Age is also strongly correlated with development of hypertension in OC users. Women who previously have had hypertension during pregnancy may be more likely to develop elevation of blood pressure on OC's. Hypertension that develops as a result of taking OC's usually returns to normal after discontinuing the drug.

9. *Headache*—Onset or exacerbation of migraine or development of headache of a new pattern which is recurrent, persistent, or severe, requires discontinuation of OC's and evaluation of the cause.

10. *Bleeding Irregularities*—Breakthrough bleeding, spotting, and amenorrhea are frequent reasons for patients discontinuing OC's. In breakthrough bleeding, as in all cases of irregular vaginal bleeding, nonfunctional causes should be borne in mind. In undiagnosed persistent or recurrent abnormal bleeding from the vagina, adequate diagnostic measures are indicated to rule out pregnancy or malignancy. If pathology has been excluded, time or change to another OC may solve the problem. Changing to an OC with a higher estrogen content, while potentially useful in minimizing menstrual irregularity, should be done only if necessary, since this may increase risk of thromboembolic disease. Women with past history of oligomenorrhea or secondary amenorrhea or young women without regular cycles may have a tendency to remain anovulatory or to become amenorrheic after discontinuing OC's. Women with these pre-existing problems should be advised of this possibility and encouraged to use other methods. Post-use anovulation, possibly prolonged, may also occur in women without previous irregularities.

11. *Ectopic Pregnancy*—Ectopic as well as intrauterine pregnancy may occur in contraceptive failures.

12. *Breast-feeding*—OC's given in the postpartum period may interfere with lactation and decrease quantity and quality of breast milk. Furthermore, a small fraction of the hormones in OC's has been identified in the milk of mothers on OC's; effects, if any, on the breast-fed child have not been determined. If feasible, defer OC's until infant has been weaned.

Precautions—GENERAL—1. A complete medical and family history should be taken prior to initiation of OC's. Pretreatment and periodic physical examinations should include special reference to blood pressure, breasts, abdomen and pelvic organs, including Pap smear and relevant laboratory tests. As a general rule OC's should not be prescribed for longer than 1 year without another physical examination.

2. Under influence of estrogen-progestogen preparations, pre-existing uterine leiomyomata may increase in size.

3. Patients with history of psychic depression should be carefully observed and the drug discontinued if depression recurs to a serious degree. Patients becoming significantly depressed while on OC's should stop OC's and use an alternate method to try to determine whether the symptom is drug-related.

4. OC's may cause some degree of fluid retention. They should be prescribed with caution, and only with careful monitoring, in patients with conditions which might be aggravated by fluid retention, such as convulsive disorders, migraine syndrome, asthma, or cardiac or renal insufficiency.

5. Patients with a past history of jaundice during pregnancy have an increased risk of recurrence while on OC's. If jaundice develops, OC's should be discontinued.

6. Steroid hormones may be poorly metabolized in patients with impaired liver function and should be administered with caution.

7. OC users may have disturbances in normal tryptophan metabolism which may result in a relative pyridoxine deficiency. Clinical significance is undetermined.

8. Serum folate levels may be depressed by OC's. Since the pregnant woman is predisposed to development of folate deficiency and incidence of folate deficiency increases with increasing gestation, it is possible that if a woman becomes pregnant shortly after stopping OC's, she may have a greater chance of developing folate deficiency and complications attributed to this deficiency.

9. The pathologist should be advised of OC therapy when relevant specimens are submitted.

10. Certain endocrine- and liver-function tests and blood components may be affected by estrogen-containing OC's: a. Increased sulfobromophthalein retention. b. Increased prothrombin and factors VII, VIII, IX, and X; decreased antithrombin 3; increased norepinephrine-induced platelet aggregability. c. Increased thyroid-binding globulin (TBG) leading to increased circulating total-thyroid hormone, as measured by protein-bound iodine (PBI), T4 by column, or T4 by radioimmunoassay. Free T3 resin uptake is decreased, reflecting the elevated TBG; free T4 concentration is unaltered. d. Decreased pregnanediol excretion. e. Reduced response to metyrapone test.

Information for the Patient—See Patient Package Labeling.

Drug Interactions—Reduced efficacy and increased incidence of breakthrough bleeding have been associated with concomitant use of rifampin. A similar association has been suggested with barbiturates, phenylbutazone, phenytoin sodium, ampicillin and tetracycline.

Carcinogenesis—See Warnings on carcinogenic potential of OC's.

Pregnancy—Category X. See Contraindications, Warnings.

Nursing Mothers—See Warnings.

Adverse Reactions—An increased risk of these serious adverse reactions has been associated with use of OC's (see Warnings): thrombophlebitis; pulmonary embolism; coronary thrombosis; cerebral thrombosis; cerebral hemorrhage; hypertension; gallbladder disease; benign hepatomas; congenital anomalies. There is evidence of an association between the following conditions and use of OC's although additional confirmatory studies are needed: mesenteric thrombosis; neuro-ocular lesions, e.g., retinal thrombosis and optic neuritis.

The following adverse reactions have been reported in patients on OC's and are believed to be drug-related: Nausea and/or vomiting, usually the most common adverse reactions, occur in approximately 10 percent or less of patients during the first cycle. Other reactions, as a general rule, are seen much less frequently or only occasionally. Gastrointestinal symptoms (such as abdominal cramps and bloating); breakthrough bleeding; spotting; change in menstrual flow; dysmenorrhea, amenorrhea during and after treatment; temporary infertility after discontinuance of treatment; edema; chloasma or melasma which may persist; breast changes: tenderness, enlargement, and secretion; change in weight (increase or decrease); change in cervical erosion and cervical secretion; possible diminution in lactation when given immediately postpartum; cholestatic jaundice; migraine; increase in size of uterine leiomyomata; rash (allergic); mental depression; reduced tolerance to carbohydrates; vaginal candidiasis; change in corneal curvature (steepening); intolerance to contact lenses.

The following adverse reactions have been reported in users of OC's, and the association has been neither confirmed nor refuted: premenstrual-like syndrome, cataracts, changes in libido, chorea, changes in appetite, cystitis-like syndrome, headache, nervousness, dizziness, hirsutism, loss of scalp hair, erythema multiforme, erythema nodosum, hemorrhagic eruption, vaginitis, porphyria.

Acute Overdose—Serious ill effects have not been reported following acute ingestion of large doses of OC's by young children. Overdosage may cause nausea, and withdrawal bleeding may occur in females.

LO/OVRAL® each tablet contains 0.3 mg norgestrel with 0.03 mg ethinyl estradiol.

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The Physicians' Champion

In 1975... The medical profession was a punching bag. The "malpractice crisis" staggered doctors with successive blows... more and more lawsuits ...bigger judgments... and, soaring insurance premiums.

But, physicians fought back with the "Spirit of '75."

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SCPIE is the physicians' champion... medal winner in their fight for independence. Insuring more Southern California physicians than any other professional liability company. With more real muscle (assets) than any other physician-owned company in the state. Doctors working together to help doctors.

That's the spirit of '75.

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Sponsored by SOCAP

The medical associations and societies of Kern County, Los Angeles County, Orange County, San Bernardino County, San Luis Obispo County, Santa Barbara County, Ventura County.

"I can do things that I couldn't do for 3 yrs. including joining the human race again."

Quotes from an unsolicited letter received by Pfizer from an angina patient. While this patient's experience is representative of many unsolicited comments received, not all patients will respond to Procardia nor will they all respond to the same degree.

"My daily routine consisted of sitting in my chair trying to stay alive."

"My doctor switched me to PROCARDIA[*] *as soon as it became available. The change in my condition is remarkable."*

"I shop, cook and can plant flowers again."

"I have been able to do volunteer work...and feel needed and useful once again."

PROCARDIA can mean the return to a more normal life for your patients—having fewer anginal attacks,[1] taking fewer nitroglycerin tablets,[2] doing more, and being more productive once again.

Side effects are usually mild (most frequently reported are dizziness or lightheadedness, peripheral edema, nausea, weakness, headache and flushing, each occurring in about 10% of patients, transient hypotension in about 5%, palpitation in about 2% and syncope in about 0.5%).

for the varied faces of angina

* Procardia is indicated for the management of:
1) Confirmed vasospastic angina.
2) Angina where the clinical presentation suggests a possible vasospastic component.
3) Chronic stable angina without evidence of vasospasm in patients who remain symptomatic despite adequate doses of beta blockers and or nitrates or who cannot tolerate these agents. In chronic stable angina (effort-associated angina) PROCARDIA has been effective in controlled trials of up to eight weeks' duration in reducing angina frequency and increasing exercise tolerance, but confirmation of sustained effectiveness and evaluation of long-term safety in these patients are incomplete.

PROCARDIA®
(NIFEDIPINE) *Capsules 10 mg*

Please see PROCARDIA *brief summary on adjoining page.*

In clinical anxiety,

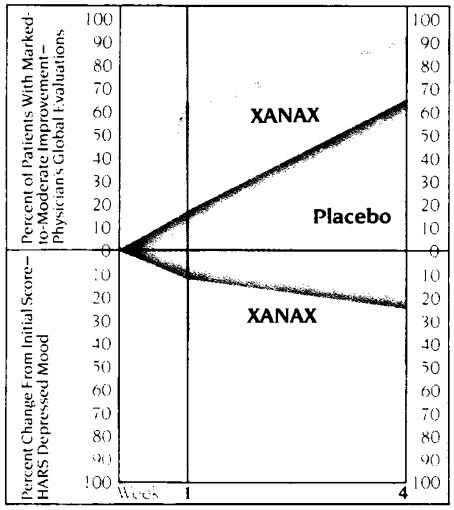
Upjohn THE UPJOHN COMPANY
Kalamazoo, Michigan 49001 USA

depressive symptoms are part of the picture in 7 out of 10 geriatrics.

The geriatric profile of XANAX can help.

In a recent clinical study* of 83 geriatric patients with clinical anxiety, 73% were diagnosed as also having symptoms of depressed mood.

XANAX is well suited for therapy because it demonstrates greater efficacy than placebo in reducing the overall Hamilton Anxiety Rating Scale Total Score by significantly reducing individual items including depressed mood (see Figure).



A desirable profile of clinical advantages

- **Rapidly relieves** the symptoms of anxiety including depressed mood
- **No clinically significant ECG changes** over the course of therapy
- **Relieves the symptoms of insomnia** significantly better than placebo
- Drowsiness is the most frequently reported adverse effect
- **Simple geriatric dosage**—0.25 mg, two or three times daily

*Data on file The Upjohn Company

Please see next page for brief summary of prescribing information.

Xanax® 0.25 mg Tablets
alprazolam C-IV

(Continued from Page 488)

A SUCCESSFUL AND GROWING "old time GP" practice in beautiful sunny Santa Barbara. Must leave $130,000 gross for family reasons. (805) 965-9500.

CALIFORNIA AND WESTERN STATES. HIGH INCOME practices for sale: Endocrinology, Radiology, Nephrology, Neurosurgery, Invasive and non-Invasive Cardiology, OB/GYN, Psychiatry, Internal, Family, Pediatric, Surgery, others. Mary Bradshaw, Professional Practice Opportunities, 21 Altamount Drive, Orinda, CA 94563; (415) 376-0762. Sales, Appraisals, Consulting, Placement, Résumé preparation service.

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RICHMOND AREA: Practice for sale: FP or Internist, luxurious, good location, in front of a hospital, 35 minutes from San Francisco. Contact (415) 341-2530 after 6 pm.

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URGENT CARE CENTERS—Excellent opportunity for Board certified Family Physician, Internist or ER Physician with 3 years experience. Full or part-time practice in centers operated by national hospital chain now developing new subsidiary in Southern California. Competitive salary plus incentive and fringe benefits. Send CV to: Dr Charles Magee, 9681 Hidden Farm Road, Alta Loma, CA 91701, or call: (714) 980-2226.

INTERNIST WANTS TO BUY Internal Medicine practice in a town of 25,000 or more population. Please call (606) 832-4404 after 5 pm; or Box 6418, Western Journal of Medicine, 44 Gough St, San Francisco, CA 94103.

HEMATOLOGIST-ONCOLOGIST/INTERNIST seeks hospital-based practice. Northern California, L.A. area preferred. Available August 1984. CV upon request at Box 6417, Western Journal of Medicine, 44 Gough St, San Francisco, CA 94103.

CLASSIFIED INFORMATION

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SPOKANE MEDICAL SUITES AVAILABLE 605-1,050 sq. ft. Fully serviced building: pharmacy, path-lab, x-ray, dispensing optician, physical therapist, dental lab, restaurant, conference room, vault. Supporting practices. Ample parking for patients and staff. Adjacent to hospital. Medical Center Building-Kiemle & Hagood Co., Property Managers, West 601 Main Avenue, Spokane, WA 99201; (509) 838-6541.

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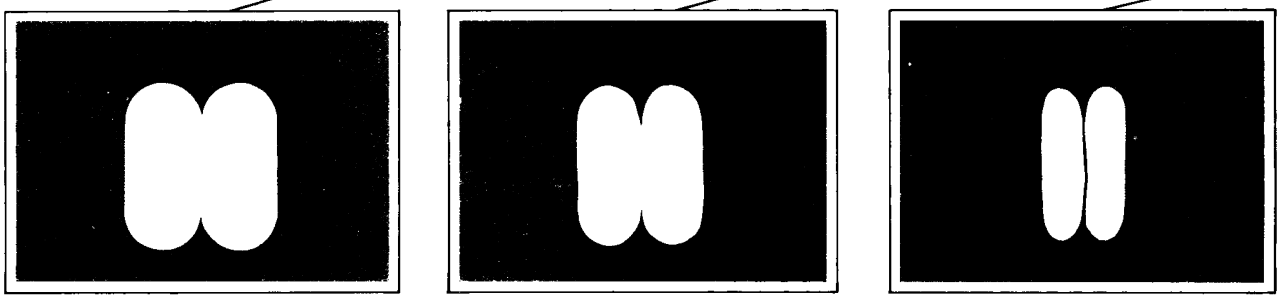

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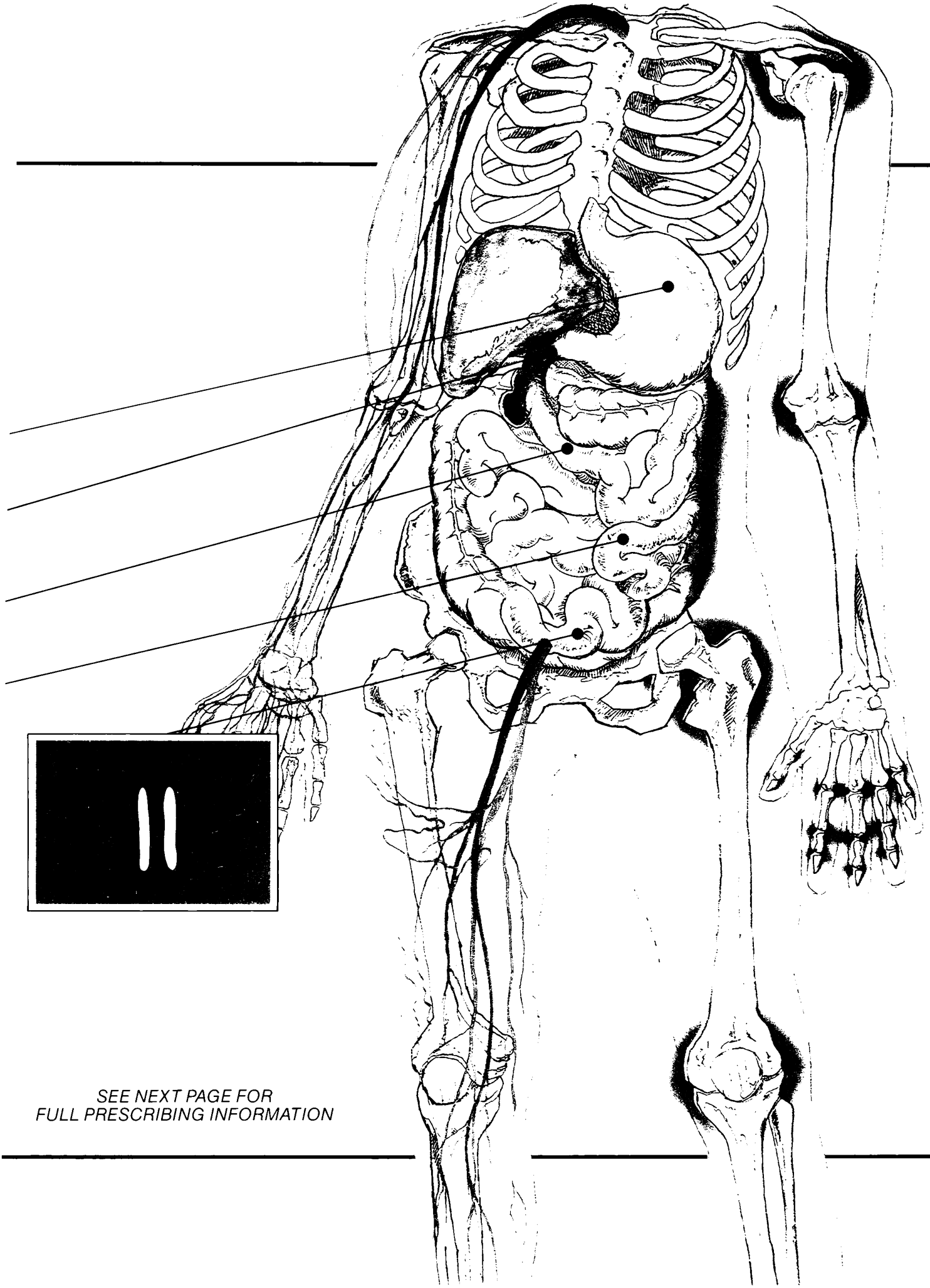


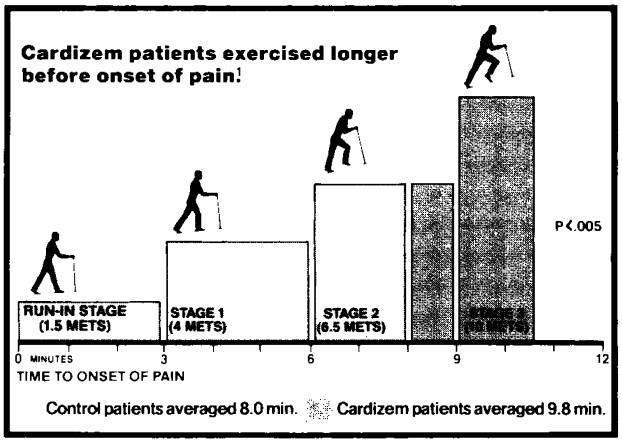
SEE NEXT PAGE FOR
FULL PRESCRIBING INFORMATION

cardizem™
(diltiazem HCl)
30 mg and 60 mg tablets

INCREASES EXERCISE TOLERANCE, REDUCES ANGINAL FREQUENCY* WITH A LOW INCIDENCE OF SIDE EFFECTS

Calcium channel blockade with CARDIZEM™ (diltiazem HCl) produces changes in cardiovascular hemodynamics and coronary blood flow that are of benefit in myocardial ischemia.

CARDIZEM™ (diltiazem HCl) ALLOWS PATIENTS TO SIGNIFICANTLY PROLONG EXERCISE TOLERANCE, EVEN IN DEMANDING BRUCE PROTOCOL EXERCISE TESTS[1] (n = 15)†



This study is of special significance because patients not only exercised longer but *to the next higher stage* in the Bruce protocol.

A Bruce protocol with a run-in stage was used for all tests. Each stage lasts three minutes.

In other studies, Cardizem produced 41% to 68% reduction of Prinzmetal's variant angina attacks[2]

†This study is a report from one center in a multicenter study.

Therapy with Cardizem produced a low incidence of side effects.

In placebo-controlled trials (222 patients) conducted in the United States, the incidence of adverse reactions reported during Cardizem therapy was not greater than that reported during placebo therapy.

Those adverse reactions reported most frequently with Cardizem in 959 patients in controlled and uncontrolled U.S. trials have been:

- Nausea 2.7%
- Swelling/edema 2.4%
- Arrhythmia 2.0%
- Headache 2.0%
- Rash 1.8%
- Fatigue 1.1%

Other reactions reported infrequently (less than 1%) are listed in full prescribing information on adjacent page.

References:

1. Pool PE, Seagren SC, Bonanno JA, et al: The treatment of exercise-inducible chronic stable angina with diltiazem: Effect on treadmill exercise. *Chest* 78 (July suppl): 234-238, 1980.
2. Schroeder JS, Feldman RL, Giles TD, et al: Multiclinic controlled trial of diltiazem for Prinzmetal's angina. *Am J Med* 72:227-232, 1982.

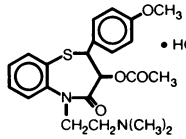
**Please see adjacent page for full prescribing information.*

PROFESSIONAL USE INFORMATION

cardizem™
(diltiazem HCl)
30 mg and 60 mg tablets

DESCRIPTION

CARDIZEM™ (diltiazem hydrochloride) is a calcium ion influx inhibitor (slow channel blocker or calcium antagonist). Chemically, diltiazem hydrochloride is 1,5-Benzothiazepin-4(5H)one,3-(acetyloxy)-5-[2-(dimethylamino)ethyl]-2,3-dihydro-2-(4-methoxyphenyl)-, monohydrochloride,(+) -cis-. The chemical structure is:



Diltiazem hydrochloride is a white to off-white crystalline powder with a bitter taste. It is soluble in water, methanol, and chloroform. It has a molecular weight of 450.98. Each tablet of CARDIZEM contains either 30 mg or 60 mg diltiazem for oral administration.

CLINICAL PHARMACOLOGY

The therapeutic benefits achieved with CARDIZEM are believed to be related to its ability to inhibit the influx of calcium ions during membrane depolarization of cardiac and vascular smooth muscle.

Mechanisms of Action. Although precise mechanisms of its antianginal actions are still being delineated, CARDIZEM is believed to act in the following ways:

1. Angina Due to Coronary Artery Spasm: CARDIZEM has been shown to be a potent dilator of coronary arteries both epicardial and subendocardial. Spontaneous and ergonovine-induced coronary artery spasm are inhibited by CARDIZEM.
2. Exertional Angina: CARDIZEM has been shown to produce increases in exercise tolerance, probably due to its ability to reduce myocardial oxygen demand. This is accomplished via reductions in heart rate and systemic blood pressure at submaximal and maximal exercise work loads.

In animal models, diltiazem interferes with the slow inward (depolarizing) current in excitable tissue. It causes excitation-contraction uncoupling in various myocardial tissues without changes in the configuration of the action potential. Diltiazem produces relaxation of coronary vascular smooth muscle and dilation of both large and small coronary arteries at drug levels which cause little or no negative inotropic effect. The resultant increases in coronary blood flow (epicardial and subendocardial) occur in ischemic and nonischemic models and are accompanied by dose-dependent decreases in systemic blood pressure and decreases in peripheral resistance.

Hemodynamic and Electrophysiologic Effects. Like other calcium antagonists, diltiazem decreases sinoatrial and atrioventricular conduction in isolated tissues and has a negative inotropic effect in isolated preparations. In the intact animal, prolongation of the AH interval can be seen at higher doses.

In man, diltiazem prevents spontaneous and ergonovine-provoked coronary artery spasm. It causes a decrease in peripheral vascular resistance and a modest fall in blood pressure and, in exercise tolerance studies in patients with ischemic heart disease, reduces the heart rate/blood pressure product for any given work load. Studies to date, primarily in patients with good ventricular function, have not revealed evidence of a negative inotropic effect; cardiac output, ejection fraction, and left ventricular end diastolic pressure have not been affected. There are as yet few data on the interaction of diltiazem and beta-blockers. Resting heart rate is usually unchanged or slightly reduced by diltiazem.

Intravenous diltiazem in doses of 20 mg prolongs AH conduction time and AV node functional and effective refractory periods approximately 20%. In a study involving single oral doses of 300 mg of CARDIZEM in six normal volunteers, the average maximum PR prolongation was 14% with no instances of greater than first-degree AV block. Diltiazem-associated prolongation of the AH interval is not more pronounced in patients with first-degree heart block. In patients with sick sinus syndrome, diltiazem significantly prolongs sinus cycle length (up to 50% in some cases).

Chronic oral administration of CARDIZEM in doses of up to 240 mg/day has resulted in small increases in PR interval, but has not usually produced abnormal prolongation. There were, however, three instances of second-degree AV block and one instance of third-degree AV block in a group of 959 chronically treated patients.

Pharmacokinetics and Metabolism. Diltiazem is absorbed from the tablet formulation to about 80% of a reference capsule and is subject to an extensive first-pass effect, giving an absolute bioavailability (compared to intravenous dosing) of about 40%. CARDIZEM undergoes extensive hepatic metabolism in which 2% to 4% of the unchanged drug appears in the urine. In vitro binding studies show CARDIZEM is 70% to 80% bound to plasma proteins. Competitive ligand binding studies have also shown CARDIZEM binding is not altered by therapeutic concentrations of digoxin, hydrochlorothiazide, phenylbutazone, propranolol, salicylic acid, or warfarin. Single oral doses of 30 to 120 mg of CARDIZEM result in detectable plasma levels within 30 to 60 minutes and peak plasma levels two to three hours after drug administration. The plasma elimination half-life following single or multiple drug administration is approximately 3.5 hours. Desacetyl diltiazem is also present in the plasma at levels of 10% to 20% of the parent drug and is 25% to 50% as potent as a coronary vasodilator as diltiazem. Therapeutic blood levels of CARDIZEM appear to be in the range of 50 to 200 ng/ml. There is a departure from dose-linearity when single doses above 60 mg are given; a 120-mg dose gave blood levels three times that of the 60-mg dose. There is no information about the effect of renal or hepatic impairment on excretion or metabolism of diltiazem.

INDICATIONS AND USAGE

1. **Angina Pectoris Due to Coronary Artery Spasm.** CARDIZEM is indicated in the treatment of angina pectoris due to coronary artery spasm. CARDIZEM has been shown effective in the treatment of spontaneous coronary artery spasm presenting as Prinzmetal's variant angina (resting angina with ST-segment elevation occurring during attacks).
2. **Chronic Stable Angina (Classic Effort-Associated Angina).** CARDIZEM is indicated in the management of chronic stable angina in patients who cannot tolerate therapy with beta-blockers and/or nitrates or who remain symptomatic despite adequate doses of these agents. CARDIZEM has been effective in short-term controlled trials in reducing angina frequency and increasing exercise tolerance, but confirmation of sustained effectiveness is incomplete.

There are no controlled studies of the effectiveness of the concomitant use of diltiazem and beta-blockers or of the safety of this combination in patients with impaired ventricular function or conduction abnormalities.

CONTRAINDICATIONS

CARDIZEM is contraindicated in (1) patients with sick sinus syndrome except in the presence of a functioning ventricular pacemaker, (2) patients with second- or third-degree AV block, and (3) patients with hypotension (less than 90 mm Hg systolic).

WARNINGS

1. **Cardiac Conduction.** CARDIZEM prolongs AV node refractory periods without significantly prolonging sinus node recovery time, except in patients with sick sinus syndrome. This effect may rarely result in abnormally slow heart rates (particularly in patients with sick sinus syndrome) or second- or third-degree AV block (four of 959 patients for 0.42%). Concomitant use of diltiazem with beta-blockers or digitalis may result in additive effects on cardiac conduction. A patient with Prinzmetal's angina developed periods of asystole (2 to 5 seconds) after a single dose of 60 mg of diltiazem.
2. **Congestive Heart Failure.** Although diltiazem has a negative inotropic effect in isolated animal tissue preparations, hemodynamic studies in humans with normal ventricular function have not shown a reduction in cardiac index nor consistent negative effects on contractility (dp/dt). Experience with the use of CARDIZEM alone or in combination with beta-blockers in patients with impaired ventricular function is very limited. Caution should be exercised when using the drug in such patients.
3. **Hypotension.** Decreases in blood pressure associated with CARDIZEM therapy may occasionally result in symptomatic hypotension.
4. **Acute Hepatic Injury.** There has been a single report in a patient receiving 120 mg of diltiazem tid of marked transaminase elevation (SGOT 4500, SGPT 2300) accompanied by hyperbilirubinemia (to 3 mg%), occurring after four days of treatment. The enzyme abnormalities resolved entirely, and enzymes were nearly normal a week after cessation of treatment. No rechallenge was carried out, but the patient had no evidence of viral hepatitis and received no other drugs but isosorbide dinitrate.

   No other similar liver injury has been reported in clinical trials, but marketing experience in Europe has resulted in a rechallenge-confirmed instance of hepatocellular injury. However, it should be noted that there have been further episodes of raised transaminases in the absence of diltiazem in this patient, so that the relationship to diltiazem of the abnormalities is not completely clear. Other instances of transaminase elevation have been reported in Europe, but their relationship to the drug is uncertain.

PRECAUTIONS

General. CARDIZEM is extensively metabolized by the liver and excreted by the kidneys and in bile. As with any new drug given over prolonged periods, laboratory parameters should be monitored at regular intervals. The drug should be used with caution in patients with impaired renal or hepatic function. In subacute and chronic dog and rat studies designed to produce toxicity, high doses of diltiazem were associated with hepatic damage. In special subacute hepatic studies, oral doses of 125 mg/kg and higher in rats were associated with histological changes in the liver which were reversible when the drug was discontinued. In dogs, doses of 20 mg/kg were also associated with hepatic changes; however, these changes were reversible with continued dosing.

Drug Interaction. Pharmacologic studies indicate that there may be additive effects in prolonging AV conduction when using beta-blockers or digitalis concomitantly with CARDIZEM. (See WARNINGS.)

Uncontrolled domestic studies suggest that concomitant use of CARDIZEM and beta-blockers or digitalis is usually well tolerated. Available data are not sufficient, however, to predict the effects of concomitant treatment, particularly in patients with left ventricular dysfunction or cardiac conduction abnormalities; the effect of diltiazem on serum digoxin levels has not been examined. The safety of the combination of CARDIZEM and beta-blockers or digitalis is currently being investigated in well-controlled studies.

Carcinogenesis, Mutagenesis, Impairment of Fertility. A 24-month study in rats and a 21-month study in mice showed no evidence of carcinogenicity. There was also no mutagenic response in in vitro bacterial tests. No intrinsic effect on fertility was observed in rats.

Pregnancy. Category C. Reproduction studies have been conducted in mice, rats, and rabbits. Administration of doses ranging from five to ten times greater (on a mg/kg basis) than the daily recommended therapeutic dose has resulted in embryo and fetal lethality. These doses, in some studies, have been reported to cause skeletal abnormalities. In the perinatal/postnatal studies, there was some reduction in early individual pup weights and survival rates. There was an increased incidence of stillbirths at doses of 20 times the human dose or greater.

There are no well-controlled studies in pregnant women; therefore, use CARDIZEM in pregnant women only if the potential benefit justifies the potential risk to the fetus.

Nursing Mothers. It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, exercise caution when CARDIZEM is administered to a nursing woman if the drug's benefits are thought to outweigh its potential risks in this situation.

Pediatric Use. Safety and effectiveness in children have not been established.

ADVERSE REACTIONS

Serious adverse reactions have been rare in studies carried out to date, but it should be recognized that patients with impaired ventricular function and cardiac conduction abnormalities have usually been excluded. Experience with an added beta-blocker is also extremely limited.

In domestic placebo-controlled trials, the incidence of adverse reactions reported during CARDIZEM therapy was not greater than that reported during placebo therapy.

In addition, the following have been reported infrequently and represent occurrences which can be at least reasonably associated with the pharmacology of calcium influx inhibition. In many cases, the relationship to CARDIZEM has not been established. The most common occurrences, as well as their frequency of presentation, are nausea (2.7%), swelling/edema (2.4%), arrhythmia (2.0%), headache (2.0%), rash (1.8%), and fatigue (1.1%). In addition, the following events were reported infrequently (<1.0%). The order of presentation corresponds to the relative frequency of occurrence.

Cardiovascular:	Flushing, congestive heart failure, bradycardia, hypotension, syncope, pounding heart.
Central Nervous System:	Drowsiness, dizziness, lightheadedness, nervousness, depression, weakness, insomnia, confusion, hallucinations.
Gastrointestinal:	Vomiting, diarrhea, gastric upset, constipation, indigestion, pyrosis.
Dermatologic:	Pruritus, petechiae, urticaria.
Other:	Photosensitivity, nocturia, thirst, paresthesias, polyuria, osteoarticular pain.

The following additional experiences have been noted:

A patient with Prinzmetal's angina experiencing episodes of vasospastic angina developed periods of transient asymptomatic asystole approximately five hours after receiving a single 60-mg dose of CARDIZEM.

Experience in 959 patients taking oral doses of CARDIZEM resulted in three cases (0.31%) of second-degree AV block and one case (0.10%) of third-degree AV block at doses of 240 to 360 mg daily.

In rare instances, mild to moderate transient elevations of alkaline phosphatase, SGOT, SGPT, LDH, and CPK have been noted during CARDIZEM therapy. A single incident of markedly elevated liver enzymes associated with symptoms was reported in a patient taking 360 mg per day for four days. Drug was discontinued and enzymes normalized within 1 week.

OVERDOSAGE OR EXAGGERATED RESPONSE

Overdosage experiences with oral diltiazem have not been reported. Single oral doses of 300 mg of CARDIZEM have been well tolerated by healthy volunteers. In the event of overdosage or exaggerated response, appropriate supportive measures should be employed in addition to gastric lavage. The following measures may be considered:

Bradycardia	Administer atropine (0.60 to 1.0 mg). If there is no response to vagal blockade, administer isoproterenol cautiously.
High-degree AV Block	Treat as for bradycardia above. Fixed high-degree AV block should be treated with cardiac pacing.
Cardiac Failure	Administer inotropic agents (isoproterenol, dopamine, or dobutamine) and diuretics.
Hypotension	Vasopressors (eg, dopamine or levarterenol bitartrate).

Actual treatment and dosage should depend on the severity of the clinical situation and the judgment and experience of the treating physician.

The oral LD_{50}'s in mice and rats range from 415 to 740 mg/kg and from 560 to 810 mg/kg, respectively. The intravenous LD_{50}'s in these species were 60 and 38 mg/kg, respectively. The oral LD_{50} in dogs is considered to be in excess of 50 mg/kg, while lethality was seen in monkeys at 360 mg/kg. The toxic dose in man is not known, but blood levels in excess of 800 ng/ml have not been associated with toxicity.

DOSAGE AND ADMINISTRATION

Exertional Angina Pectoris Due to Atherosclerotic Coronary Artery Disease or Angina Pectoris at Rest Due to Coronary Artery Spasm. Dosage must be adjusted to each patient's needs. Starting with 30 mg four times daily, before meals and at bedtime, dosage should be increased gradually to 240 mg (given in divided doses three or four times daily) at one- to two-day intervals until optimum response is obtained. The effectiveness and safety of dosages exceeding 240 mg per day are currently being investigated. There are no available data concerning dosage requirements in patients with impaired renal or hepatic function. If the drug must be used in such patients, titration should be carried out with particular caution.

Concomitant Use With Other Antianginal Agents.

1. **Sublingual NTG** may be taken as required to abort acute anginal attacks during CARDIZEM therapy.
2. **Prophylactic Nitrate Therapy**—CARDIZEM may be safely coadministered with short- and long-acting nitrates, but there have been no controlled studies to evaluate the antianginal effectiveness of this combination.
3. **Beta-blockers.** (See WARNINGS and PRECAUTIONS.)

HOW SUPPLIED

CARDIZEM 30-mg tablets are supplied in bottles of 100 (NDC 0088-1771-47). Each green tablet is engraved with MARION on one side and 1771 engraved on the other. CARDIZEM 60-mg scored tablets are supplied in bottles of 100 (NDC 0088-1772-47). Each yellow tablet is engraved with MARION on one side and 1772 on the other.

Issued 11/82

Another patient benefit product from

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MARION LABORATORIES, INC.
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3/83

Photo: Peter B. Kaplan

If you still believe in me, save me.

For nearly a hundred years, the Statue of Liberty has been America's most powerful symbol of freedom and hope. Today the corrosive action of almost a century of weather and salt air has eaten away at the iron framework; etched holes in the copper exterior.

On Ellis Island, where the ancestors of nearly half of all Americans first stepped onto American soil, the Immigration Center is now a hollow ruin.

Inspiring plans have been developed to restore the Statue and to create on Ellis Island a permanent museum celebrating the ethnic diversity of this country of immigrants. But unless restoration is begun now, these two landmarks in our nation's heritage could be closed at the very time America is celebrating their hundredth anniversaries. The 230 million dollars needed to carry out the work is needed now.

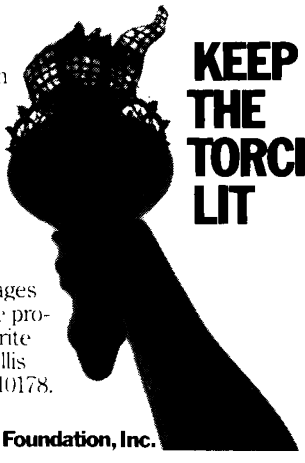
All of the money must come from private donations; the federal government is not raising the funds. This is consistent with the Statue's origins. The French people paid for its creation themselves. And America's businesses spearheaded the public contributions that were needed for its construction and for the pedestal.

The torch of liberty is everyone's to cherish. Could we hold up our heads as Americans if we allowed the time to come when she can no longer hold up hers?

Opportunities for Your Company.

OFFICIAL SPONSOR LIBERTY

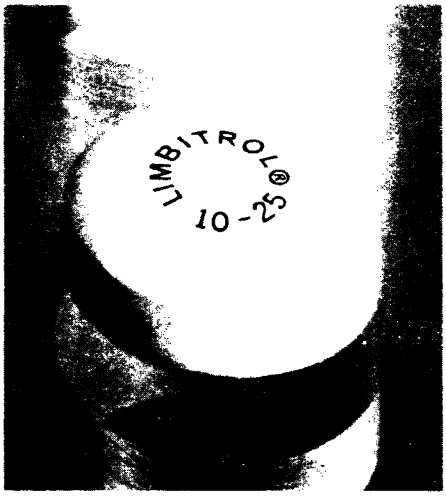
You are invited to learn more about the advantages of corporate sponsorship during the nationwide promotions surrounding the restoration project. Write on your letterhead to: The Statue of Liberty-Ellis Island Foundation, Inc., 101 Park Ave, N.Y., N.Y. 10178.



KEEP THE TORCH LIT

Save these ornaments. Send your personal tax-deductible donation to: P.O. Box 2986, New York, N.Y. 10019. **The Statue of Liberty-Ellis Island Foundation, Inc.**

The specific fit for anxious depression



Uniquely specific...Limbitrol is the only agent that treats anxious depression with amitriptyline and the specific anxiolytic action of Librium® (chlordiazepoxide HCl/Roche).

Rapid onset...Patients taking Limbitrol in a multicenter study[1] achieved 62% of their overall four-week improvement in the first week.

Dramatic reduction of somatic symptoms...Early, middle and late insomnia associated with anxious depression dropped 91%, 87% and 89% respectively after only two weeks of Limbitrol therapy. GI complaints associated with anxious depression dropped 73% after two weeks, and headaches decreased 79% in two weeks, 88% in four weeks.[2]

Documented effect on mood ...including marked improvement in the first week with regard to psychic and somatic anxiety, guilt, anorexia and insomnia.[2]

Superior compliance...which can be seen as a result of the early and broad symptom relief of Limbitrol; insomnia (late and middle), agitation, psychic and somatic anxiety, hypochondriasis and feelings of worthlessness are usually reduced within the first week of therapy as measured on the Hamilton Depression Scale.[1]

***h.s.* dosage for most patients**...with flexible dosage schedules for all patients, including *t.i.d.* and combined *h.s.*/a.m. doses.

Low cardiotoxicity...Only 1.9% of the patients in two multicenter studies reported cardiovascular side effects.[2]

Few side effects and few dropouts...Only 4% of the Limbitrol patients dropped out of therapy because of side effects, while 13% of the amitriptyline patients dropped out.[1]

Patients should be cautioned about the combined effects of Limbitrol and alcohol and other CNS depressants and about activities requiring complete mental alertness, such as operating machinery or driving a car.

References: 1. Feighner JP *et al*: *Psychopharmacology 61*:217-225, Mar 22, 1979.
2. Data on file, Hoffmann-La Roche Inc., Nutley, NJ.

In moderate depression and anxiety

Limbitrol® IV

Tablets 5-12.5 each containing 5 mg chlordiazepoxide and 12.5 mg amitriptyline (as the hydrochloride salt)
Tablets 10-25 each containing 10 mg chlordiazepoxide and 25 mg amitriptyline (as the hydrochloride salt)

Before prescribing, please consult complete product information, a summary of which follows:
Indications: Relief of moderate to severe depression associated with moderate to severe anxiety.
Contraindications: Known hypersensitivity to benzodiazepines or tricyclic antidepressants. Do not use with monoamine oxidase (MAO) inhibitors or within 14 days following discontinuation of MAO inhibitors since hyperpyretic crises, severe convulsions and deaths have occurred with concomitant use; then initiate cautiously, gradually increasing dosage until optimal response is achieved. Contraindicated during acute recovery phase following myocardial infarction.
Warnings: Use with great care in patients with history of urinary retention or angle-closure glaucoma. Severe constipation may occur in patients taking tricyclic antidepressants and anticholinergic-type drugs. Closely supervise cardiovascular patients. (Arrhythmias, sinus tachycardia and prolongation of conduction time reported with use of tricyclic antidepressants, especially high doses. Myocardial infarction and stroke reported with use of this class of drugs.) Caution patients about possible combined effects with alcohol and other CNS depressants and against hazardous occupations requiring complete mental alertness (e.g., operating machinery, driving).
***Usage in Pregnancy*: Use of minor tranquilizers during the first trimester should almost always be avoided because of increased risk of congenital malformations as suggested in several studies. Consider possibility of pregnancy when instituting therapy; advise patients to discuss therapy if they intend to or do become pregnant.**
Since physical and psychological dependence to chlordiazepoxide have been reported rarely, use caution in administering Limbitrol to addiction-prone individuals or those who might increase dosage; withdrawal symptoms following discontinuation of either component alone have been reported (nausea, headache and malaise for amitriptyline; symptoms [including convulsions] similar to those of barbiturate withdrawal for chlordiazepoxide).
Precautions: Use with caution in patients with a history of seizures, in hyperthyroid patients or those on thyroid medication, and in patients with impaired renal or hepatic function. Because of the possibility of suicide in depressed patients, do not permit easy access to large quantities in these patients. Periodic liver function tests and blood counts are recommended during prolonged treatment. Amitriptyline component may block action of guanethidine or similar antihypertensives. Concomitant use with other psychotropic drugs has not been evaluated; sedative effects may be additive. Discontinue several days before surgery. Limit concomitant administration of ECT to essential treatment. See Warnings for precautions about pregnancy. Limbitrol should not be taken during the nursing period. Not recommended in children under 12. In the elderly and debilitated, limit to smallest effective dosage to preclude ataxia, oversedation, confusion or anticholinergic effects.
Adverse Reactions: Most frequently reported are those associated with either component alone: drowsiness, dry mouth, constipation, blurred vision, dizziness and bloating. Less frequently occurring reactions include vivid dreams, impotence, tremor, confusion and nasal congestion. Many depressive symptoms including anorexia, fatigue, weakness, restlessness and lethargy have been reported as side effects of both Limbitrol and amitriptyline. Granulocytopenia, jaundice and hepatic dysfunction have been observed rarely.
The following list includes adverse reactions not reported with Limbitrol but requiring consideration because they have been reported with one or both components or closely related drugs:
Cardiovascular: Hypotension, hypertension, tachycardia, palpitations, myocardial infarction, arrhythmias, heart block, stroke.
Psychiatric: Euphoria, apprehension, poor concentration, delusions, hallucinations, hypomania and increased or decreased libido.
Neurologic: Incoordination, ataxia, numbness, tingling and paresthesias of the extremities, extrapyramidal symptoms, syncope, changes in EEG patterns.
Anticholinergic: Disturbance of accommodation, paralytic ileus, urinary retention, dilatation of urinary tract.
Allergic: Skin rash, urticaria, photosensitization, edema of face and tongue, pruritus.
Hematologic: Bone marrow depression including agranulocytosis, eosinophilia, purpura, thrombocytopenia.
Gastrointestinal: Nausea, epigastric distress, vomiting, anorexia, stomatitis, peculiar taste, diarrhea, black tongue.
Endocrine: Testicular swelling and gynecomastia in the male, breast enlargement, galactorrhea and minor menstrual irregularities in the female and elevation and lowering of blood sugar levels.
Other: Headache, weight gain or loss, increased perspiration, urinary frequency, mydriasis, jaundice, alopecia, parotid swelling.
Overdosage: Immediately hospitalize patient suspected of having taken an overdose. Treatment is symptomatic and supportive. I.V. administration of 1 to 3 mg physostigmine salicylate has been reported to reverse the symptoms of amitriptyline poisoning. See complete product information for manifestation and treatment.
Dosage: Individualize according to symptom severity and patient response. Reduce to smallest effective dosage when satisfactory response is obtained. Larger portion of daily dose may be taken at bedtime. Single *h.s.* dose may suffice for some patients. Lower dosages are recommended for the elderly.
Limbitrol 10-25, initial dosage of three to four tablets daily in divided doses, increased up to six tablets or decreased to two tablets daily as required. Limbitrol 5-12.5, initial dosage of three to four tablets daily in divided doses, for patients who do not tolerate higher doses.
How Supplied: White, film-coated tablets, each containing 10 mg chlordiazepoxide and 25 mg amitriptyline (as the hydrochloride salt) and blue, film-coated tablets, each containing 5 mg chlordiazepoxide and 12.5 mg amitriptyline (as the hydrochloride salt)—bottles of 100 and 500; Tel-E-Dose® packages of 100; Prescription Paks of 50.

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